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Self-Assessment in Neonatal Perinatal Medicine

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And for inviting us to present this session

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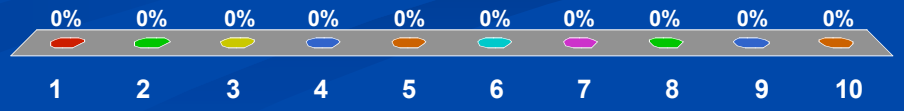
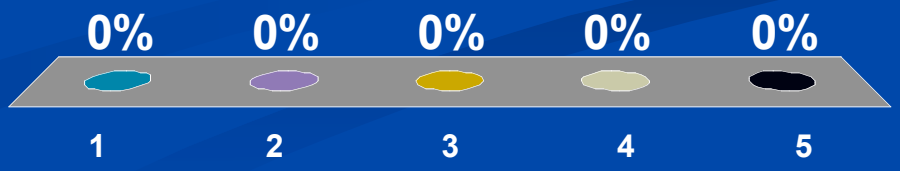
You are a

- Medical student
- Pediatric resident
- Pediatrician
- NPM fellow
- NPM
- Advance practice nurse
- Other physician
- Other nurse
- Housekeeping staff
- Other

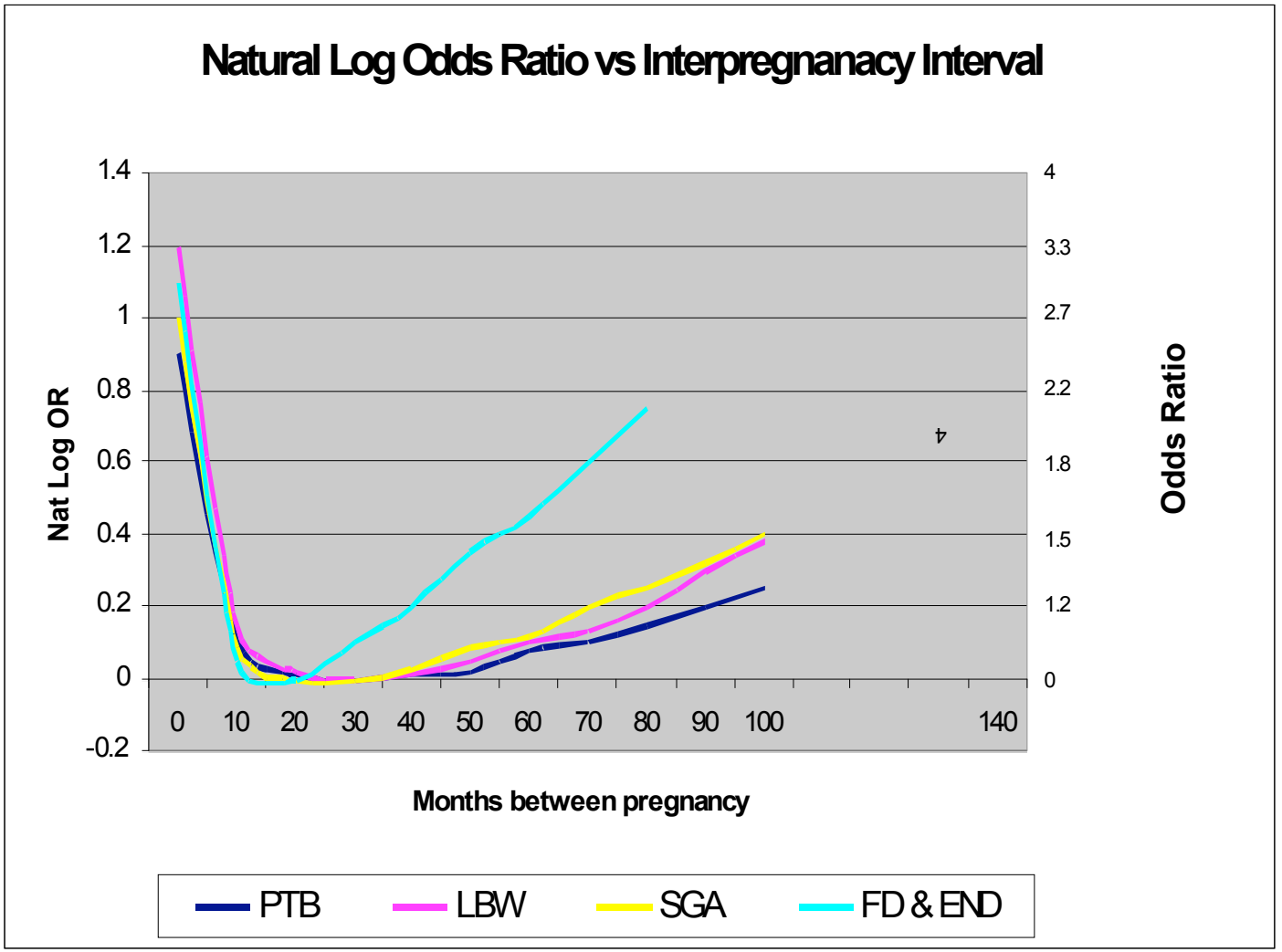


Pregnancy spacing & pregnancy outcome: Optimal perinatal outcomes would be expected with interpregnancy intervals to be:

1. < 20 months
2. ★ 20 to 40 months
3. ★ 40 to 60 months
4. > 60 months
5. Doesn't matter



Optimal pregnancy spacing



NR+10/06 (7)

In the first week after home birth (no prenatal care), she developed this rash.

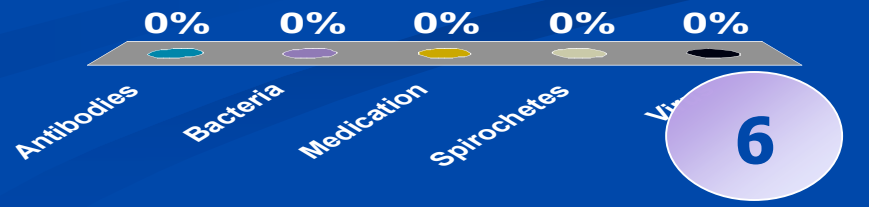
PEx: 3.5 kg; 51 cm; 33cm OFC.

HR 66; RR 40;

BP 74/45; no murmur.

This condition is due to maternally-acquired:

1. Antibodies
2. Bacteria
3. Medication
4. Spirochetes
5. Virus



Neonatal Lupus

- Criteria: cutaneous lupus &/or congenital heart block
  - Rare condition (~ 2% NLE from anti-Ro mothers)
- Heart block is the only life-threatening feature of NL
  - Neonatal cardiac morbidity or death (25%) > fetal death
- Transplacental ANTIBODIES (anti-Ro & anti-La)
  - Fibrotic replacement of SA and AV nodes; calcification +/-

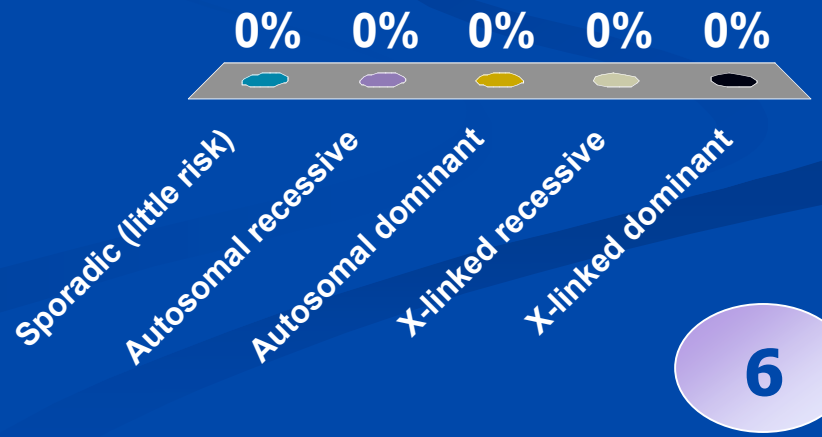
NR+3/06(3); NR+5/06(10)

What condition affects this infant?

- Achondroplasia

If a female with Achondroplasia becomes a parent [partner unaffected], what is the risk of achondroplasia in the fetus? That is, genetically, achondroplasia is

1. Sporadic (little risk)
2. Autosomal recessive
3. Autosomal dominant
4. X-linked recessive
5. X-linked dominant



Achondroplasia

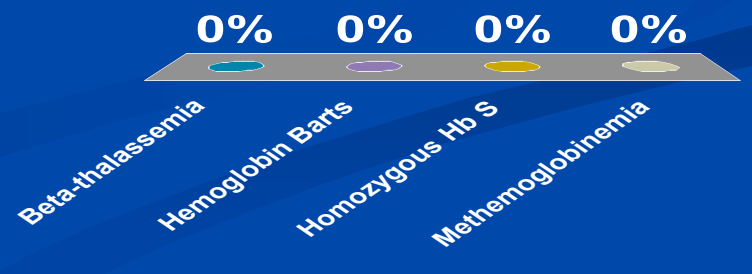
- Autosomal dominant, 80% de novo mutation, complete penetrance, 1 in 15,000 to 40,000 births
  - Advanced paternal age
  - Defect occurs during spermatogenesis
  - One of two point mutations at 4p16.3
  - <1% recurrence risk for parents
- Fetal risk with unaffected partner = 50%
- Fetal risk if partner has achondroplasia
  - ¼ homozygous (non-viable)
  - ½ (2 of 4) heterozygous for Achondroplasia & affected
    - 2/3 of live-born offspring
  - ¼ normal
    - 1/3 of live-born offspring

NR+ 5/05 (4)

Erythroblastosis, as seen here, can produce severe anemia in utero, resulting in hepatosplenomegaly, hydrops, and later neonatal severe jaundice.

If hydrops were detected prenatally, and blood typing/antibodies, TORCH & parvovirus are negative:
Which condition below is associated with severe, early-onset, often fatal hydrops?

1. Beta-thalassemia
2. Hemoglobin Barts
3. Homozygous Hb S
4. Methemoglobinemia



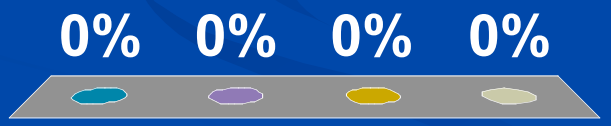
Hemoglobinopathies

- Alpha chain:
  - Clinical picture depends on # of gene deletions
  - 4-gene deletion→ Hb Barts
    - No Alpha chains
    - Gamma4 tetramers
    - High O2 affinity→ tissue hypoxia, CHF, edema, death in utero
  - 1-gene deletion
    - Alpha thalassemia carrier
  - 2-gene deletion
    - Alpha thalassemia trait
      - Microcytosis @ birth
  - 3-gene deletion
    - Hbg H disease
      - Microcytic, hemolytic anemia
- Beta chain
  - Hbg A
    - Reciprocal of gamma
    - B-Thalassemia = impaired beta chain synthesis
  - Hg S: Glu→Val (6)
- Gamma chain
  - Hbg F
    - 100% @ 12 weeks
    - 85% @ 34 weeks
    - <5% @ 56 weeks
- Delta chains
  - Hbg A2
    - Trace amounts @ term
    - <2.5% in adults

NR+9/04(7)

Term female: presents with small bullae, erythematous bases, curvilinear pattern. One of two sisters had similar bullae; now sister has nail dystrophy & verrucous lesions. Brothers are OK. Diagnosis most consistent?

1. Cutaneous mastocytosis
2. Epidemolysis bullosa
3. Incontenentia pigmenti
4. Urticaria pigmentosa



Cutaneous mastocyt...
Epidemolysis bullosa
Incontenentia pigmenti
Urticaria pigmentosa

Incontinentia pigmenti

Incontenentia Pigmenti

- X-linked dominant @ Xq28 or Xp11
- Affected males: lethal *in utero*
- Skin lesions first 2 weeks after birth
  - Small linear, clustered blisters, red base, on trunk, extremities or scalp
- Scarring alopecia, nail dystrophy 1st yr.
  - Retinal vascular proliferation
  - Neurological abnormalities
- Verrucous & hyper pigmented areas

NR+ 10/04(2)

Participant Scores

347.96	Participant 70
313.14	Participant 248
300	Participant 15
300	Participant 153
238.81	Participant 105

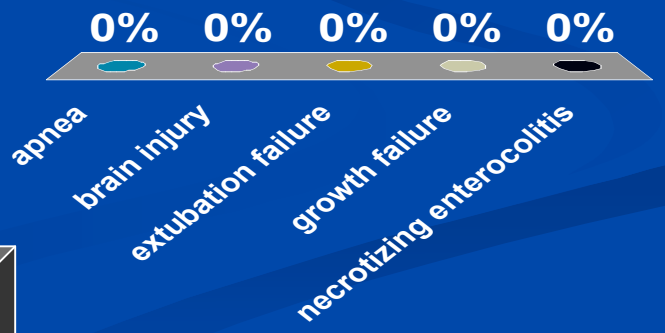
A preterm infant tolerates rapid weaning of the ventilator and is receiving minimal ventilator support on the 4th day after birth. You are considering starting prophylactic caffeine.

Of the following, the use of prophylactic caffeine in preterm infants is MOST likely to reduce the incidence of :

- apnea
- brain injury
- extubation failure
- growth failure
- necrotizing enterocolitis

Answer Now

:05



- **Caffeine and other methylxanthines:**
  - **effective in facilitating extubation in preterm infants by reducing postextubation apnea**
  - **not effective as prophylaxis to spontaneously breathing preterm infants at risk of developing apnea/bradycardia**
  - **Secondary outcomes**
    - **Slower weight gain**
    - **Fewer PDA ligations**
    - **Less BPD**
    - **Less CP**

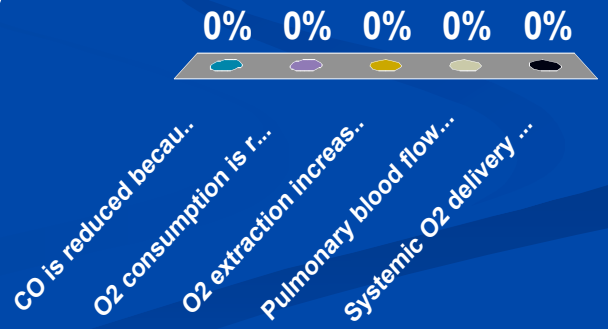
A term infant with MAS is being placed on VV ECMO.

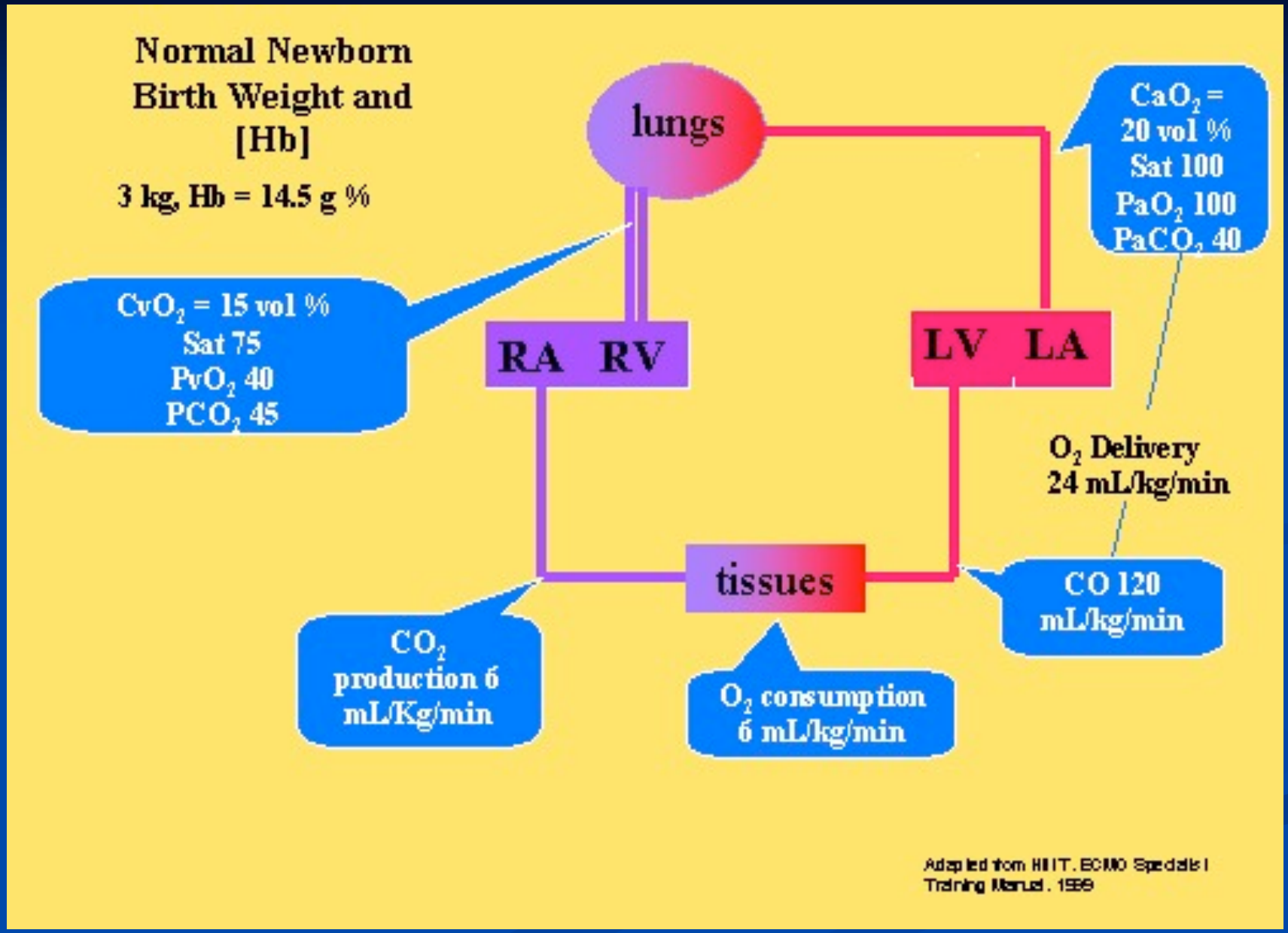
Of the following, the MOST accurate statement about the expected physiologic effects of VV ECMO is that:

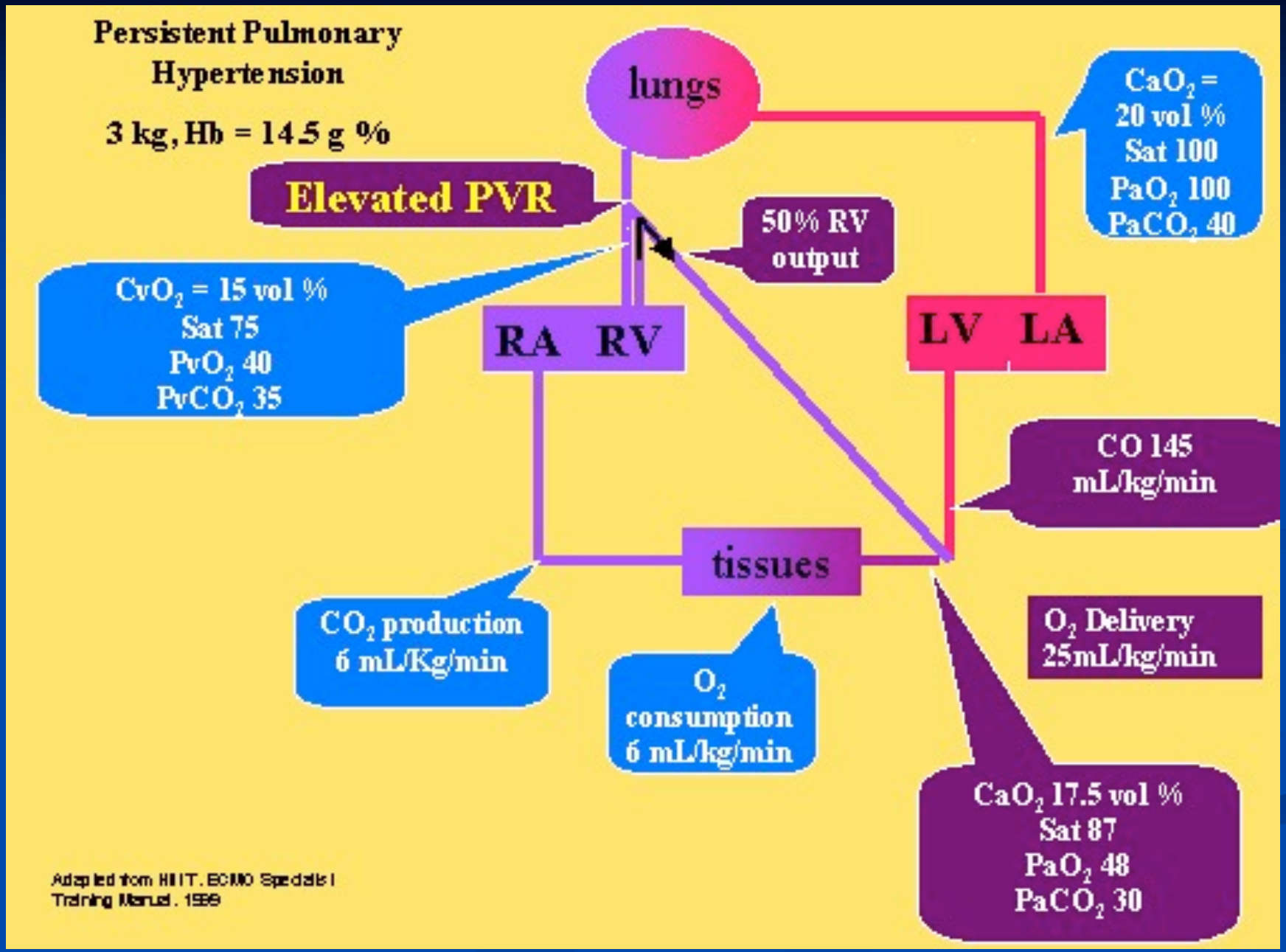
1. CO is reduced because blood flow to the coronary circulation is decreased.
2. O2 consumption is reduced because venous O2 content is increased.
3. O2 extraction increases because systemic arterial O2 content is increased.
4. Pulmonary blood flow increases because the O2 content of blood perfusing the pulmonary circulation is increased.
5. Systemic O2 delivery increases because arterial oxygen saturation is maximized (>98%).

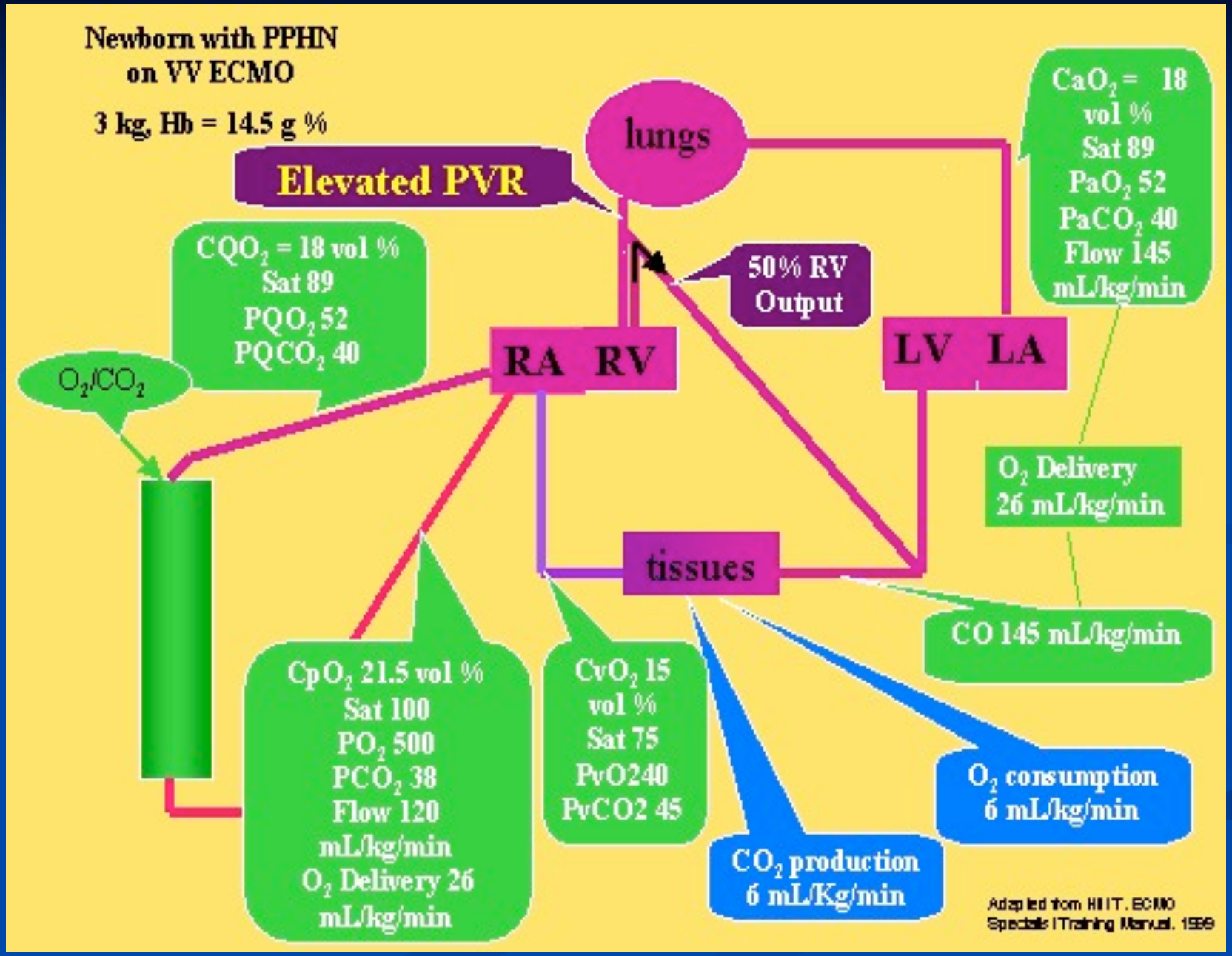
Answer Now

:05




Normal Newborn
Birth Weight and
[Hb]
3 kg, Hb = 14.5 g %
lungs
CaO2 =
20 vol %
Sat 100
PaO2 100
PaCO2 40
CvO2 = 15 vol %
Sat 75
PvO2 40
PCO2 45
RA RV
LV LA
O2 Delivery
24 mL/kg/min
tissues
CO 120
mL/kg/min
CO2
production 6
mL/Kg/min
O2 consumption
6 mL/kg/min
Adapted from HUT. ECMO Specialist
Training Manual. 1999


Persistent Pulmonary Hypertension
3 kg, Hb = 14.5 g %
lungs
Elevated PVR
50% RV output
CaO2 = 20 vol % Sat 100 PaO2 100 PaCO2 40
CvO2 = 15 vol % Sat 75 PvO2 40 PvCO2 35
RA RV
LV LA
CO 145 mL/kg/min
tissues
CO2 production 6 mL/Kg/min
O2 consumption 6 mL/kg/min
O2 Delivery 25mL/kg/min
CaO2 17.5 vol % Sat 87 PaO2 48 PaCO2 30
Adapted from HUT. ECMO Specialist Training Manual. 1999


Newborn with PPHN
on VV ECMO
3 kg, Hb = 14.5 g %
lungs
Elevated PVR
CaO_2 = 18 vol %
Sat 89
PaO_2 52
$PaCO_2$ 40
Flow 145 mL/kg/min
CQO_2 = 18 vol %
Sat 89
PQO_2 52
$PQCO_2$ 40
50% RV Output
O_2/CO_2
RA RV
LV LA
O_2 Delivery 26 mL/kg/min
tissues
CO 145 mL/kg/min
CpO_2 21.5 vol %
Sat 100
PO_2 500
PCO_2 38
Flow 120 mL/kg/min
O_2 Delivery 26 mL/kg/min
CvO_2 15 vol %
Sat 75
PvO240
PvCO2 45
O_2 consumption 6 mL/kg/min
CO_2 production 6 mL/Kg/min
Adapted from HUT. ECMO Specialist Training Manual. 1999

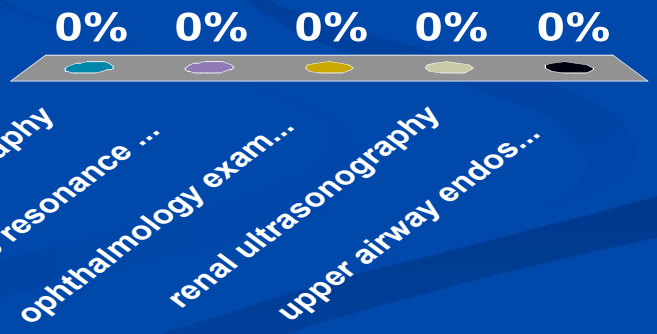
A full-term infant is born with a large, erythematous facial lesion in a beardlike distribution (Figure).

A cleft in the sternum and a supraumbilical raphe are discovered on physical examination.

Of the following, the diagnostic evaluation that RARELY uncovers an abnormality in this syndrome is:

1. echocardiography
2. magnetic resonance imaging of the brain
3. ophthalmology examination
4. renal ultrasonography
5. upper airway endoscopy

Answer Now



PHACE(S) Syndrome	
Posterior fossa abnormalities	Dandy-Walker malformation Cerebellar hypoplasia/atrophy Vermis dysgenesis/agenesis
Hemangioma	Segmental, plaque-like, facial
Arterial anomalies	Left subclavian a aneurysm Right carotid a atresia Calcified cerebral aneurysms
Cardiac anomalies	Coarctation and complex arch anomalies VSD ASD TOF
Eye defects	Microphthalmia Retinal vascular or persistent fetal vessel abnormalities Optic nerve atrophy Iris hypertropy/hypoplasia Coloboma Excavated optic disc anomalies
Sternal defects, supraumbilical raphe or both	Ventral developmental defects

- Renal defects not associated with PHACES syndrome

PHACE(S) SYNDROME

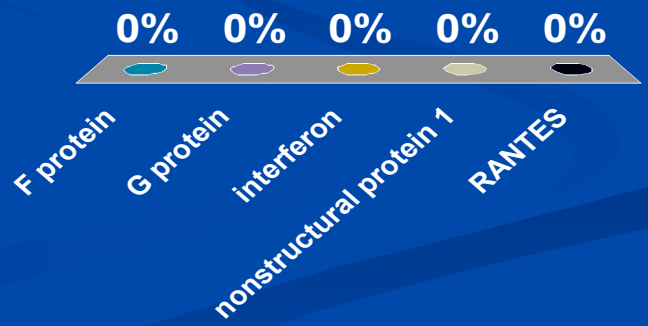
- Incidence
  - Not rare, more common than Sturge-Weber
  - 20% of facial hemangiomas
  - 2 to 3% of all hemangiomas
  - 80% female
- Hemangiomas
  - Cervicofacial mandibular, or "beard" distribution
  - May involve upper airway
- Posterior fossa abnormalities
- Developmental delay, motor delays
- Pituitary dysfunction

- Sturge-Weber syndrome:
  - Sporadic
  - Nevus flammeus of the face
  - unilateral angiomatosis of the meninges
  - vascular abnormalities of choroid vessels of eye

A 3-month-old female infant, PMA 38 weeks, has BPD. You are discussing handwashing, avoidance of crowds, and administration of palivizumab during the winter months.

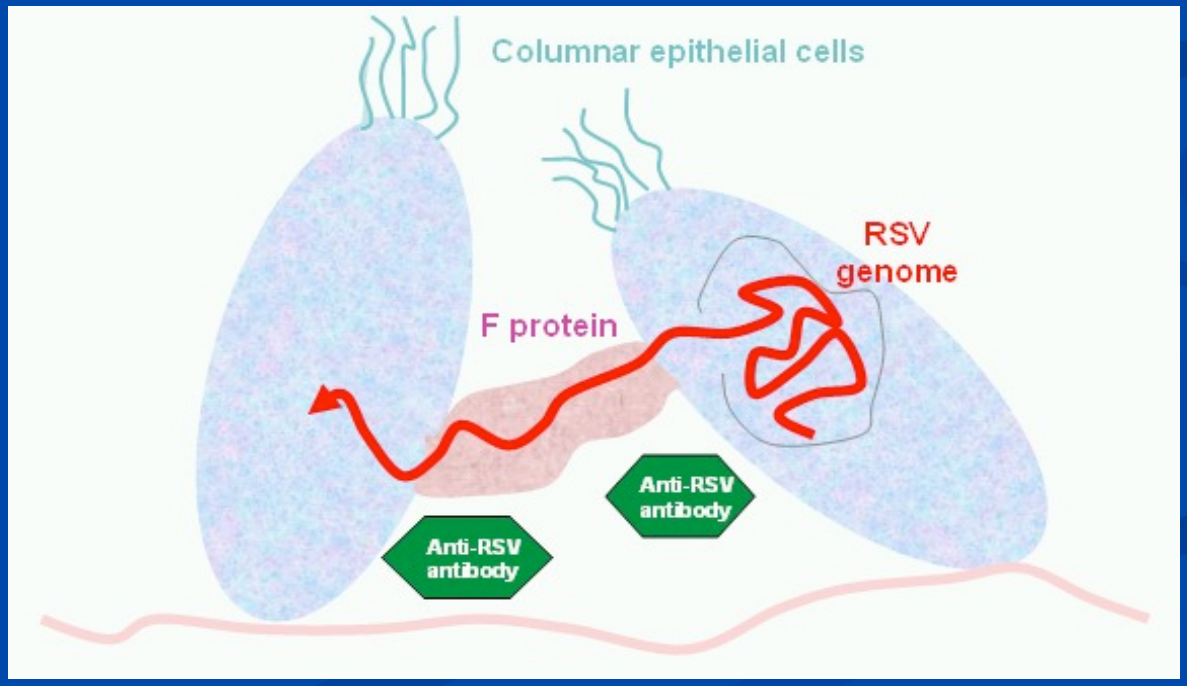
Of the following, the component of the respiratory syncytial virus that is TARGETED by palivizumab is:

1. **F protein**
2. **G protein**
3. **interferon**
4. **nonstructural protein 1**
5. **RANTES**



Answer Now

- **Respiratory Syncytial Virus (RSV)**
  - highly infectious paramyxovirus
  - related to parainfluenza, measles, and mumps viruses
- Genome: single strand of RNA with 10 genes
- Surface proteins:
  - G protein: variability of viral strains
  - F protein: cell-cell transmission of genome causes disease
    - distinct from other viruses that infect mucosa then enter blood stream to cause disease
    - Highly conserved … TARGET of palivizumab

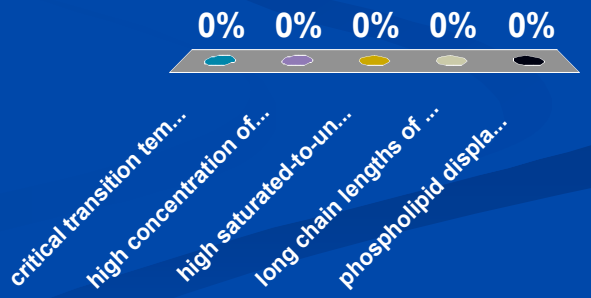


You are discussing the physical chemistry of surfactant. Of the following, a decrease in surface tension at the air-liquid interface on the alveolar surface induced by surfactant is MOST likely the result of:

- critical transition temperature below 37ºC
- high concentration of sodium and chloride in water phase
- high saturated-to-unsaturated phospholipid ratio
- long chain lengths of fatty acyl groups
- phospholipid displacement of water molecules

Answer Now

:05

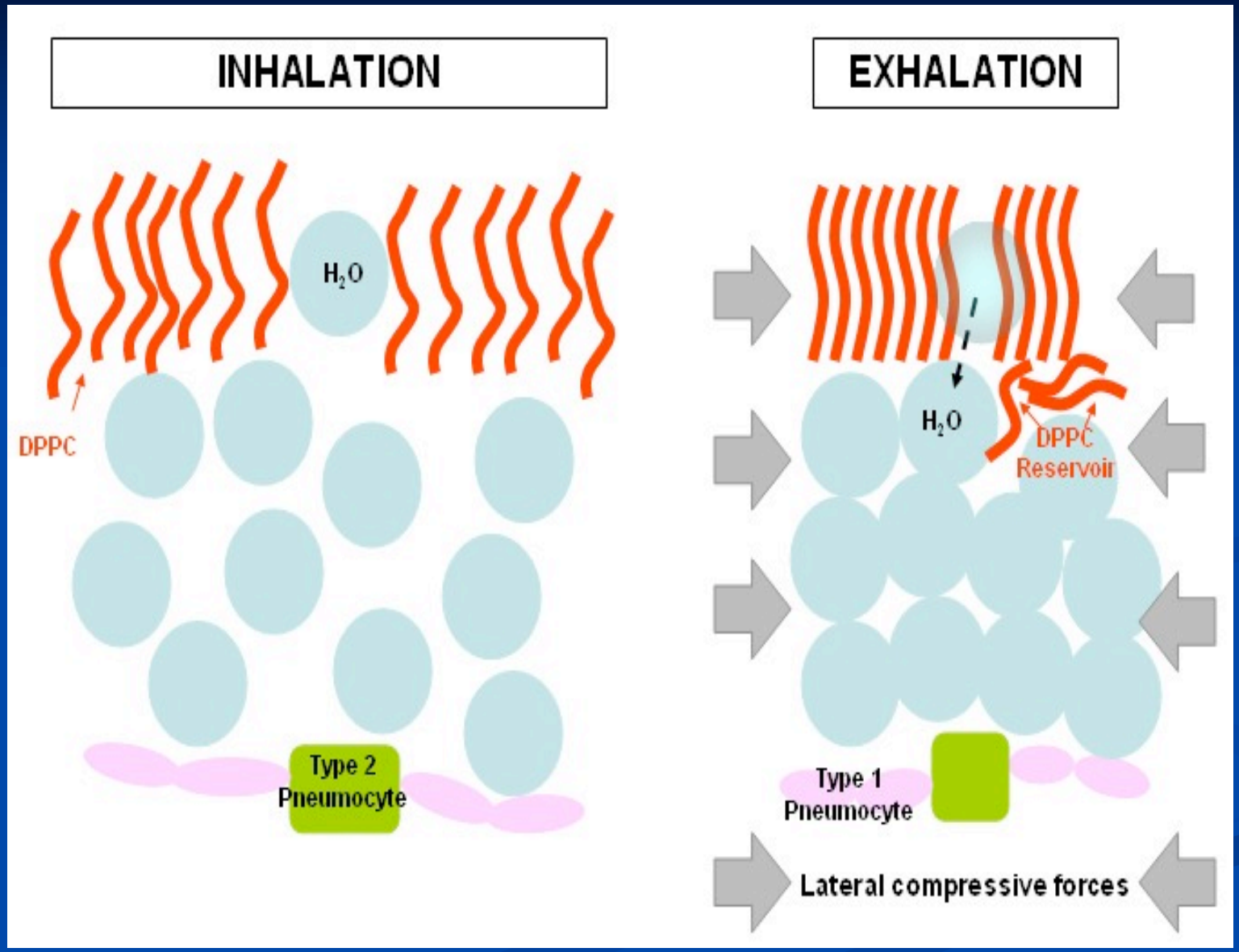


Surface tension

- Surface tension: molecules on surface of an air-liquid interface are attracted by molecules in the bulk phase of the liquid
- Net effect: surface molecules drawn into the liquid and surface area is minimized … in lung, alveoli volume is minimized and energy is required to overcome surface tension to expand the lung
- DPPC … amphipathic molecule
  - hydrophilic phosphorylcholine … liquid phase
  - hydrophobic fatty acyl group … gas phase
  - physically displaces water molecules from air-liquid surface:
    - water not attracted into liquid
    - surface tension is reduced
    - volume of gas in alveolar saccules stabilized

Surface tension

- DPPC
  - Critical transition temperature ... 41º ... nonmobile, “gel” to mobile liquid state
  - Hydration ... “gel” to liquid
  - SPB and SPC ... major influences on DPPC mobility
  - Films of DPPC ... stable at 37ºC ... easily packed to exclude water from the surface layer
    - Exhalation: compressive forces condense islands of DPPC to
      1. exclude water molecules ... lowers surface tension
      2. liquid to “gel” transition ... physical “splint” resists collapse


INHALATION
EXHALATION
H_2O
DPPC
Type 2
Pneumocyte
H_2O
DPPC
Reservoir
Type 1
Pneumocyte
Lateral compressive forces

Participant Scores

531.78	Participant 170
447.96	Participant 70
423.86	Participant 165
418.39	Participant 58
413.14	Participant 248

A male infant presents to the ED at one week of age.

- Normal birth
- Eating well
- Redness noted for past 24 hours
- Small discharge, no dimpling or edema
- Afebrile
- Vital signs normal
- WBC count normal

One week old with periumbilical rash & some discharge. Afebrile, normal vitals. These findings are most consistent with:

0% 1. neonatal tetanus

0% 2. normal cord separation

0% 3. omphalitis

0% 4. periumbilical necrotizing fasciitis

0% 5. umbilical granuloma

Answer Now

10

Omphalitis

- Most common signs
  - Redness
  - Discharge
- Causes
  - Staphylococcus aureus
  - Escherichia coli;
  - Klebsiella sp
- Systemic antibiotics
  - Erythema, edema, tender
  - Systemic signs
  - Use parenteral penicillin for Group A streptococcal infections
- Watch for progressive disease →

Periumbilical necrotizing fasciitis

- omphalitis can precede extension of signs & systemic illness
- dimpling of the skin (*peau d'orange*)
- parenteral antibiotics & surgical debridement usually required
- mortality rate ~50%

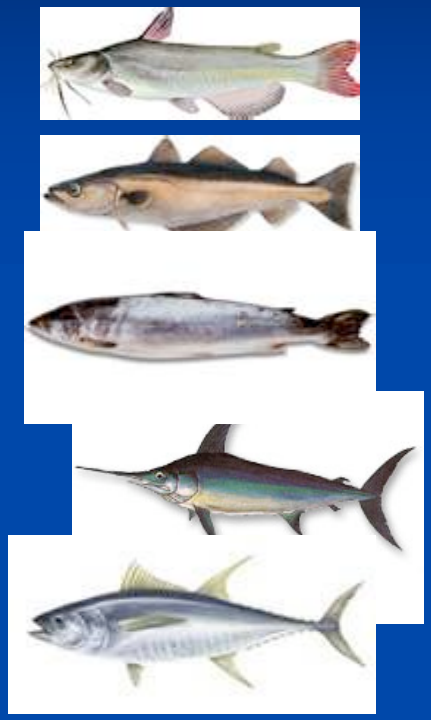
Differential diagnosis: omphalitis

1. neonatal tetanus
   Maternal Abs; irritable, poor feeder, sz.
2. normal cord separation
3. omphalitis
4. periumbilical necrotizing fasciitis
5. umbilical granuloma

Some fish contain high concentrations of methyl mercury (Hg) and should be avoided by pregnant and breastfeeding mothers.

Five popular fish.

- Catfish
- Pollack
- Salmon
- Swordfish
- Tuna



- Pregnant woman "loves fish," but heard of the concerns about mercury and other toxins.
- Any of these fish a concern?

Of the following, the fish that contains the highest concentration of methyl Hg is :

0% canned light tuna

0% catfish

0% pollock

0% salmon

0% swordfish

Answer Now

10

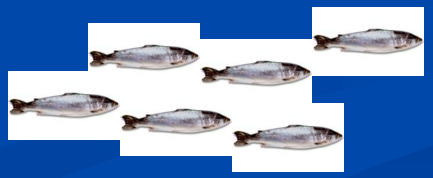
Mercury: inorganic Hg

- not toxic and absorbed poorly by the gastrointestinal tract
- enters aquatic environments as industrial pollutants …
- converted to toxic methyl Hg by aquatic vegetation

Food cycle

- fish eat contaminated vegetation
  - methyl Hg binds tightly to fish proteins
  - cooking cannot remove it
- large, long-lived, predatory fish
  swordfish, shark, king mackerel, tilefish

  - …have higher concentrations of methyl Hg in their tissues than do smaller fish



Mercury toxicity in humans

- Absorption – distribution
  - methyl Hg …fat-soluble and easily crosses the blood-brain barrier
- Clinical manifestations
  - peripheral neuropathies,
  - visual field disturbances,
  - memory loss, deafness,
  - psychiatric disturbances
  - cerebellar ataxia

Mercury in perinatal period

- methyl Hg is lipophilic
  - readily crosses the placenta and
  - enters human milk
- methyl Hg is hazardous to developing fetuses and infants …can result in
  - mental retardation,
  - seizures,
  - chorea,
  - hypersalivation,
  - deafness, and
  - blindness

You're called to the ED →

A 3-month-old term infant is brought to the hospital emergency department because of poor appetite, lethargy, weak cry, and a weak suck.

- **two weeks ago…constipated but no abnormalities were noted → use of glycerin suppositories was recommended.**
- **PE: afebrile, hypotonic and lethargic with poor head control and poor suck**
- **responsive to stimuli**
- **her eyes fail to deviate laterally on head movement**

The management element MOST likely to ameliorate this child's condition is:

1. aminoglycoside antibiotic
2. equine-derived antibodies
3. human-derived immunoglobulin
4. penicillin
5. tincture of time

Answer Now

Infant botulism

- Treatment:
  human-derived botulism immune globulin (BabyBIG)

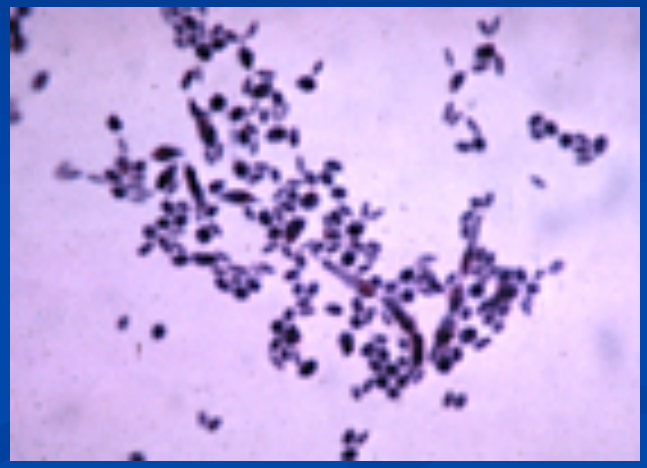
- Mortality ~15%
  no patients in the studies of BabyBIG died

Precautions:

- Antibiotics (such as penicillin or metronidazole) against *C botulinum* contraindicated
  - lysis of killed organisms → augmented neurotoxin release
- Aminoglycosides (for "suspected sepsis") → worsening neuromuscular blockade

A 21-day-old infant presents with fever

- CSF shows gram-positive diplococci …
  Streptococcus pneumoniae



- The residents inquire as to the role of *S pneumoniae* in neonatal infection, because the disease has become rare among immunized older children.

The impact of immunization of 2- to 23-month-old children against *Streptococcus pneumoniae* on the neonatal population is that:

0% 1. Antibiotic resistance has increased.
0% 2. Decreased incidence of infection among neonates
0% 3. Median onset of infection comes later in life.
0% 4. Meningitis is more prevalent.
0% 5. Racial disparity for infection has increased.

Answer Now

10

Pneumococcal vaccination

- routine immunization …2 to 23 months has resulted in a 60% decline in invasive pneumococcal disease (IPD)

- invasive disease among infants < 2 months old has decreased …herd immunity

Invasive pneumococcal disease

- clinical pattern of neonatal IPD remains unchanged—median day of onset
  - early-onset IPD continues to be the day of birth
  - late-onset IPD remains day 21
- presentation
  - bacteremia (66%)
  - pneumonitis (25%)
  - meningitis (9%)

Vaginal delivery of a term female infant

With ROM 12 hrs

- *Chlamydia* infection in second trimester:
  mother received erythromycin
- Repeat culture obtained a week before delivery positive for *Chlamydia*:
  Not re-treated before delivery
- BW 3,300 g and normal physical examination
- You are concerned about *Chlamydia* infection in the newborn because of untreated maternal *Chlamydia* infection
- What to do??

Maternal chlamydia, not treated.
Term infant delivered 12 hrs after ROM.
Of the following, the MOST appropriate course of action in this infant is:

0%	1.	conjunctival and nasopharyngeal culture
0%	2.	monitoring for signs of infection
0%	3.	oral azithromycin as a single dose
0%	4.	oral erythromycin for 14 days
0%	5.	topical erythromycin eye drops for 14 days.

Answer Now

Maternal chlamydia

- Ccurrent recommendation
  - watchful waiting and
  - treating with erythromycin only those infants who develop symptomatic *C trachomatis* infection
- Association between erythromycin treatment and development of pyloric stenosis in neonates

Participant Scores

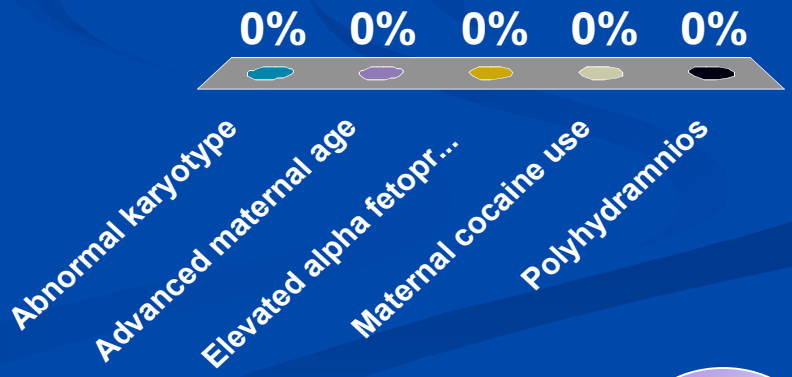
700	Participant 236
647.96	Participant 70
631.78	Participant 170
618.39	Participant 58
611.26	Participant 19

Team Scores

248.97	Medical student
240.07	Other physician
237.21	Other nurse
232.29	NPM fellow
228.02	Other

You attend the delivery of an infant at 35 weeks' gestational age. The infant appears growth restricted and presents with herniated intestines from the anterior abdominal wall (Figure). Of the following, review of this infant's prenatal history is MOST likely to reveal:

1. Abnormal karyotype
2. Advanced maternal age
3. Elevated alpha fetoprotein
4. Maternal cocaine use
5. Polyhydramnios



Gastroschisis

- Elevated maternal serum AFP (with an average elevation of >9 MOM)
  - Up to 75% of cases detected for elevated AFP
  - diagnosis by ultrasonography
- Pathogenesis:
  - vascular compromise to fetal body wall from abnormal regression of the right umbilical vein and right omphalomesenteric artery
- Incidence :
  - ~ 1 to 4 per 10,000 births
  - increasing worldwide over the past several decades
- Cause unknown—some associations (next slide)

Gastroschisis: Associations

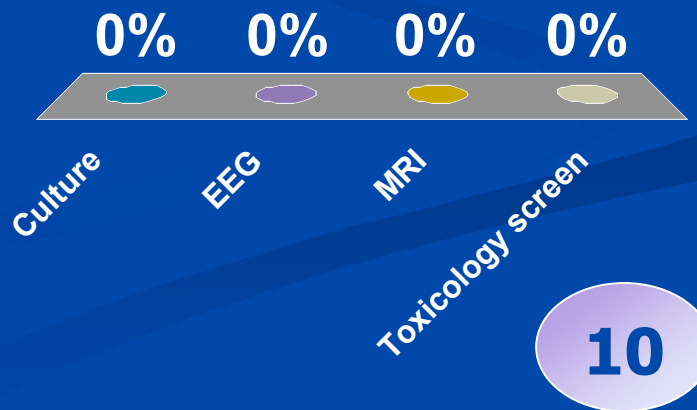
- Factors:
  - low maternal age —most consistent
  - Tobacco
  - vasoactive drug use like phenylephrine
- Non-factors:
  - Cocaine
  - advanced maternal age
  - aneuploidy or other chromosomal abnormalities
  - rarely familial

Gastroschisis: Clinical Features

- Growth restriction—70%
- Oligohydramnios-- 25%
  - polyhydramnios only with bowel atresias—20%
- Meconium- or bile-stained amniotic fluid-- 25%
- Intrauterine fetal death ~ 15%
  - in utero midgut volvulus or compromise of umbilical blood flow by the herniated bowel?
- Bowel edema and inflammatory "peel" or serositis from amniotic fluid exposure
- Mean gestational age at delivery ~ 36 weeks
- Mortality as high as 10%
  - degree of intestinal injury (short gut syndrome)
  - complications of prematurity
  - Infection
  - presence of intestinal atresias

Term female.
S/S:Alternating episodes of hyperpnea & apnea (to 25 sec).
PEx: nystagmus [not related to respiratory pattern]
F Hx: Brother (age 2) has similar pattern.
Diagnosis will be established by:

1. **Culture**
2. **EEG**
3. **MRI**
4. **Toxicology screen**

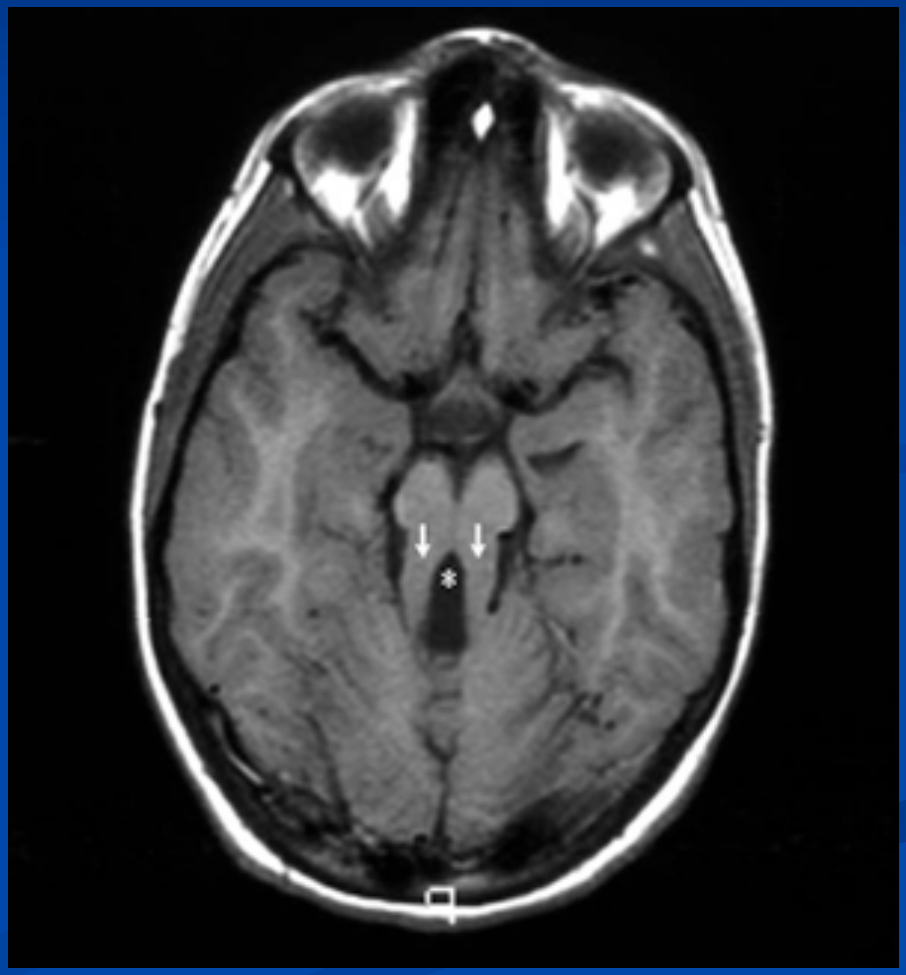


Joubert syndrome

- NB Characteristics
  - Apnea/hyperpnea
  - Eye movement disorders
  - Agenesis of cerebellar vermis
- Later:
  - Ataxia
  - Retardation
- Autosomal recessive

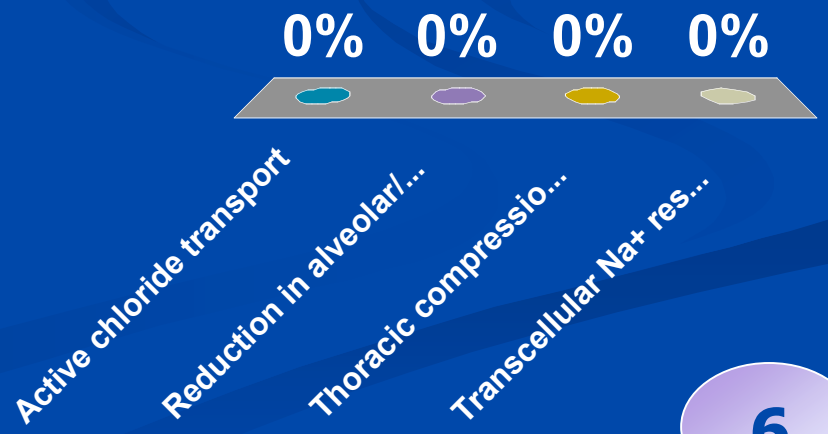
Joubert's syndrome: Molar tooth sign

- The presence of the molar tooth sign on axial MRI through the malformed pontomesencephalic junction (isthmus). The molar tooth sign consists of the following triad:
  (1) deepening of the interpeduncular fossa (*),
  (2) thick and straight superior cerebellar peduncles (arrows), and
  (3) hypoplastic vermis.



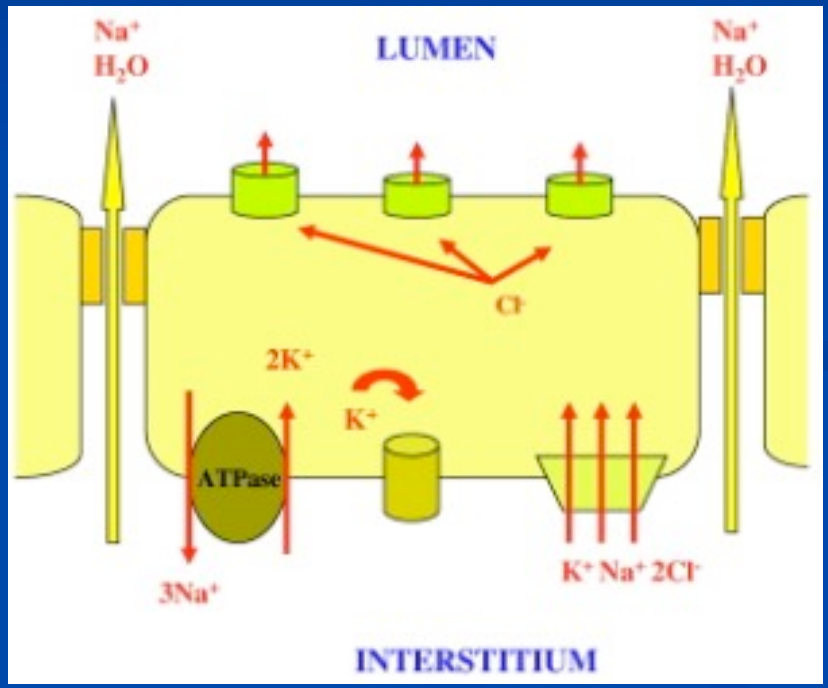
Labor most affects its decrease of pulmonary (lung) fluid volume by

1. Active chloride transport
2. Reduction in alveolar/interstitial osmotic gradients
3. Thoracic compression during vaginal passage
4. Transcellular Na+ resorption



Lung Fluid during Pregnancy

- Active secretion of fluid to maintain lung volume at functional residual capacity
- Major determinant of fetal lung growth
- Mechanism: Active chloride transport



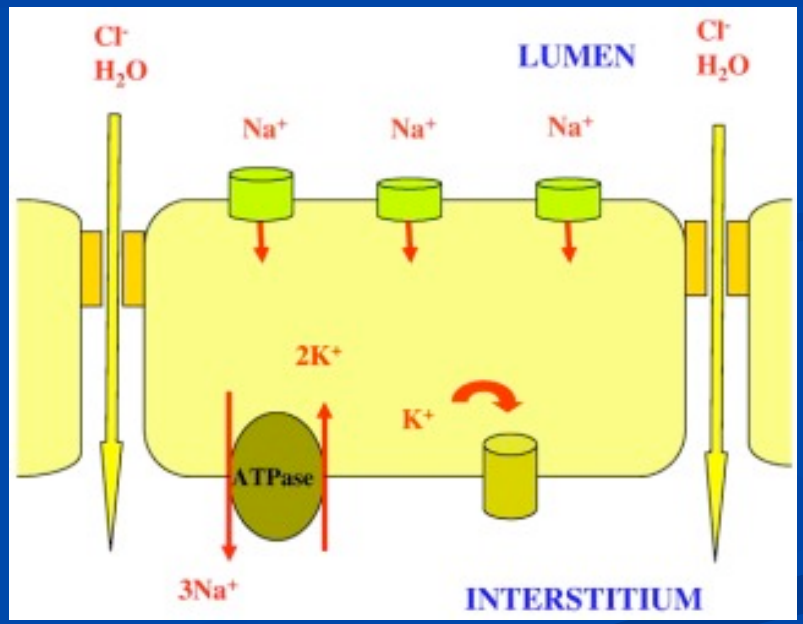
NR+ 10/06 (2)

Lung Fluid and Labor

- Active transcellular Na+ resorption
- Epinephrine surge in labor switches above "on"
  - Responsiveness increases with GA
  - Induced by thyroid & steroid hormones
  - Oxygen tension increase after birth consolidates
- Similar reduction after vaginal or cesarean after onset of labor
  - Reduced role for "squeeze"
- Mechanical (drainage) not the major factor.

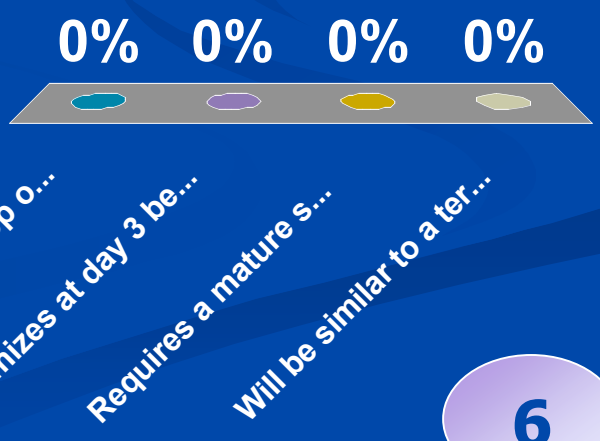
NR+ 10/06 (2)

- Fetal lung fluid resorption during labor/after delivery

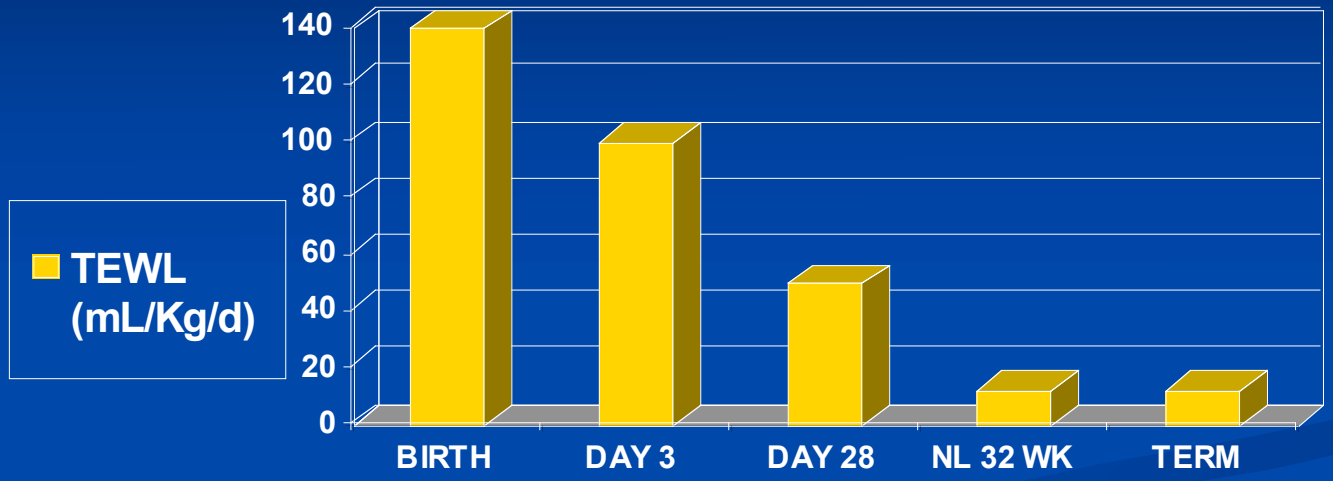


Transepidermal water loss in an infant delivered at 24 weeks' gestation, BW= 600 grams.

1. Doubles with drop of humidity from 60% to 20%
2. Maximizes at day 3 before decreasing
3. Requires a mature sweating response
4. Will be similar to a term infant's TEWL by 28 days after birth



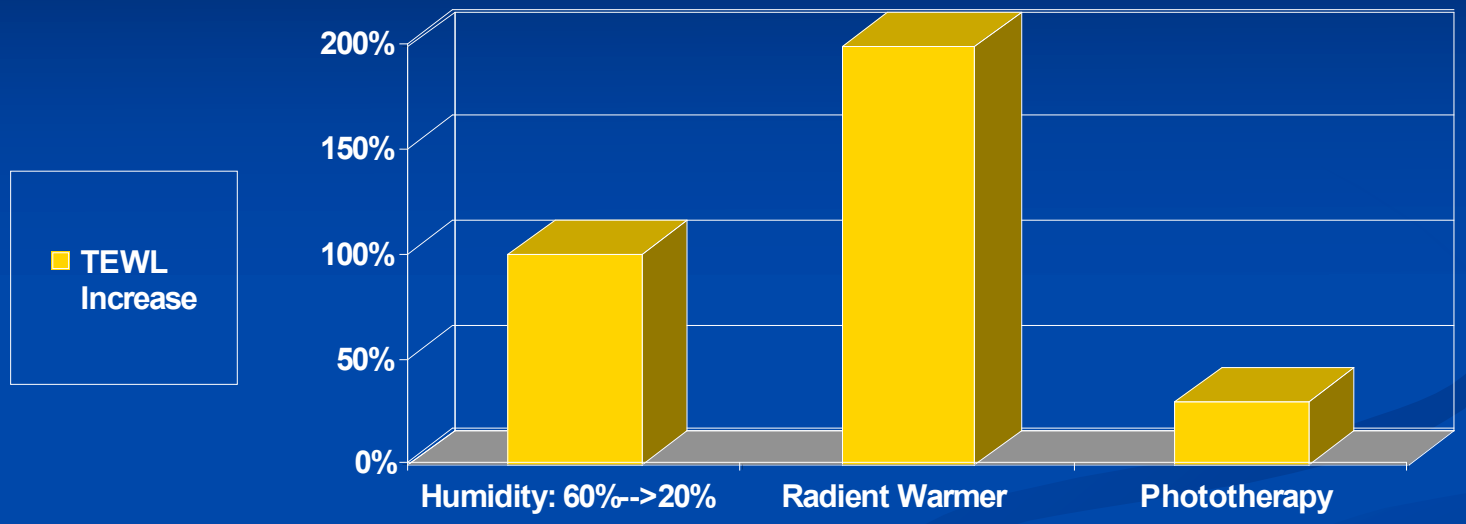
Transepidermal water loss Very Low Birth Weigh Infants



- Major determinants--neonatal
  - Gestational age
  - Post-natal age
  - Body temperature
  - Body posture

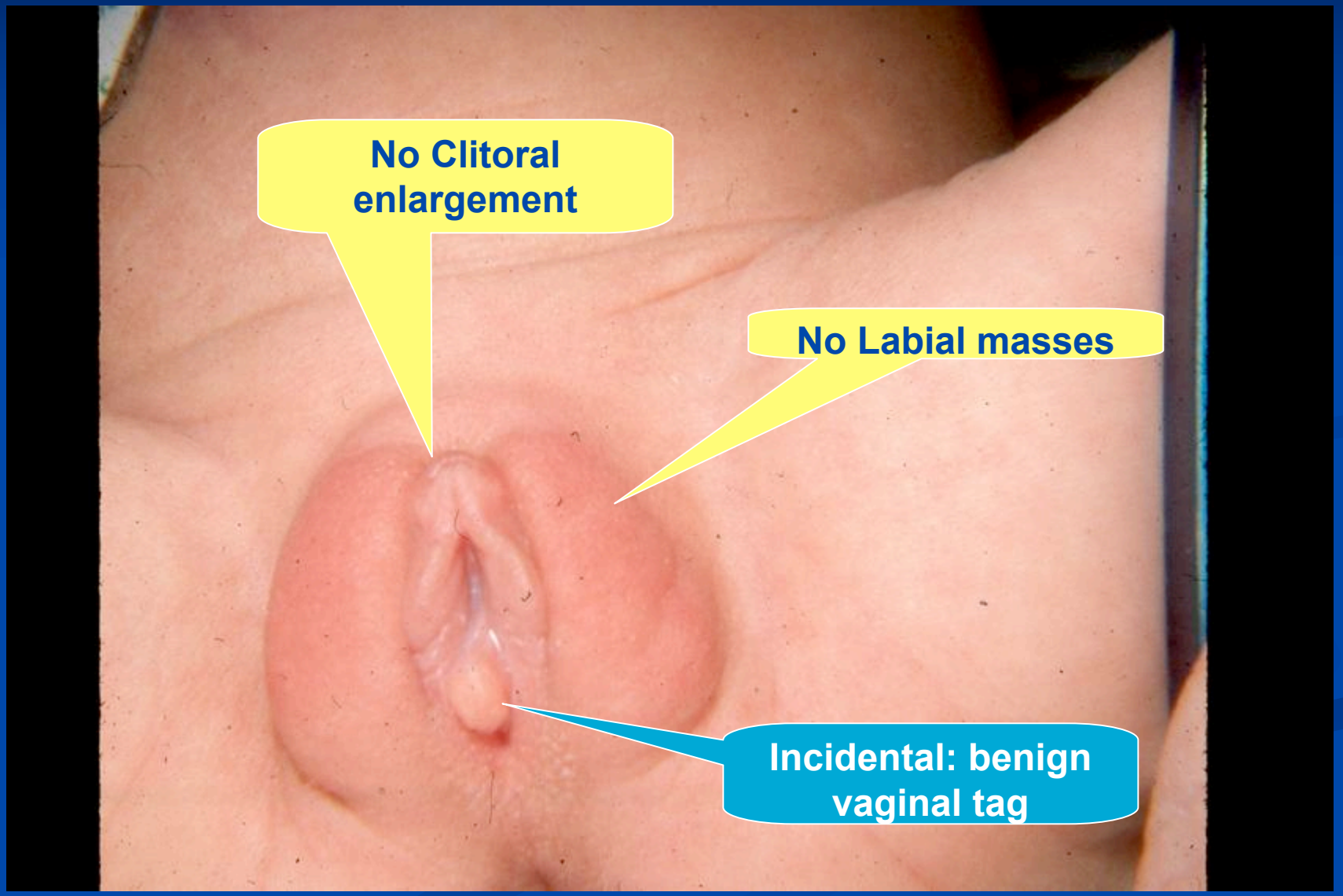
NR+7/05(10)

Transepidermal water loss Very Low Birth Weigh Infants



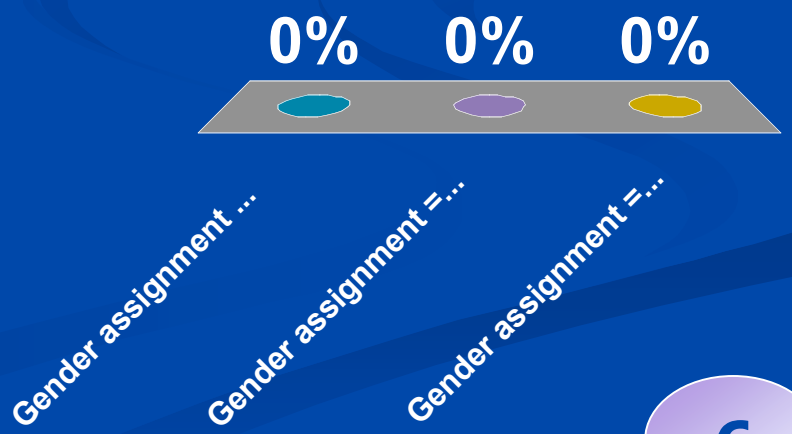
- Environmental factors affecting TEWL
  - Heat source
  - Ambient humidity
  - Phototherapy
  - Air currents

Chorionic villus sample: 46, XY
Examination at birth:



Chorionic villus karyotype: 46, XY
Uncomplicated pregnancy delivers at term.
Infant has female-appearing genitalia, no masses in labia majora, no clitoromegaly.

1. Gender assignment = male
2. Gender assignment = female
3. Gender assignment = transgender (delay to child's choice)



Gender assignment: Disorders of Sexual Development

- 46, XY with complete androgen insensitivity syndrome uniformly identify themselves as female
  - Chromosomes do not dictate assignment
- 46, XX with CAH (virilized), >90% assigned as female identify as female
- 50% of 46, XY DSD patients→ specific Dx
  - Use genital appearance, surgical options, hormonal needs, fertility potential, family & cultural views
  - Family participation, respect, confidentiality
- 46, XX patients
  - If CAH, female gender assignment is appropriate
  - If not CAH, use criteria as for 46, XY with ambiguity.
- Gender assignment in the newborn period recommended for all
  - Needs multidisciplinary team & family participation

NR+1/07(5)

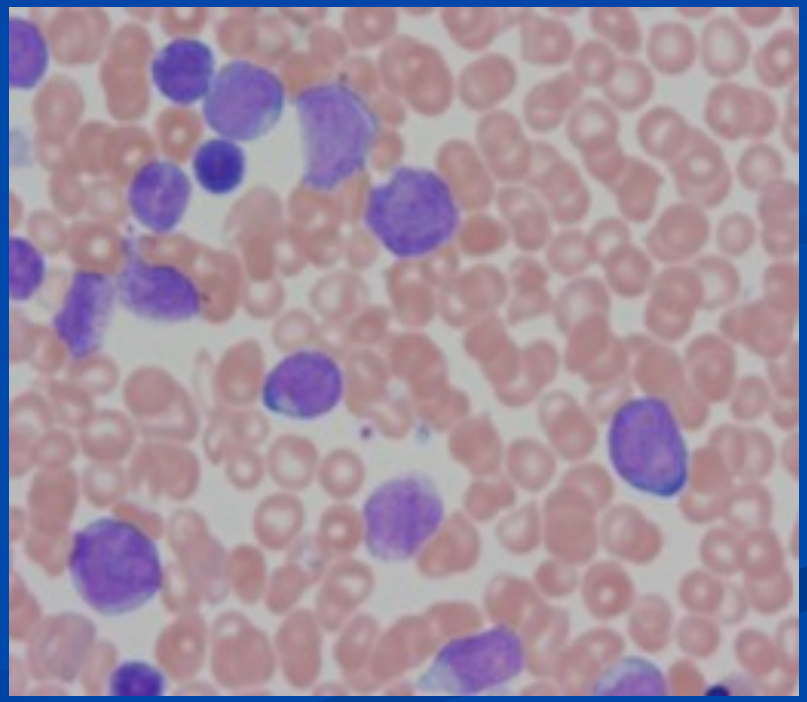
Participant Scores

749.4	Participant 236
666.22	Participant 70
654.48	Participant 170
646.89	Participant 19
619.91	Participant 58

An infant with trisomy 21 has blood drawn after birth because of respiratory distress. She has a heart murmur and marked hypotonia.

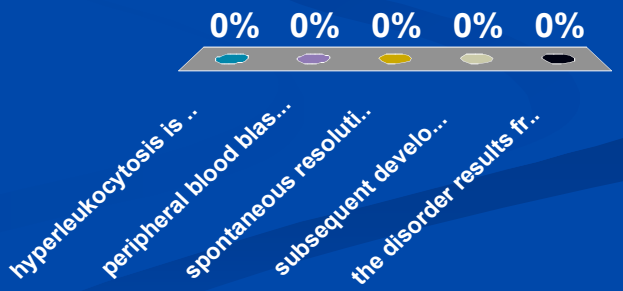
Laboratory Finding	Patient Result
WBC x 10^9/uL	134.7
Hb g/dL	13.1
Hct %	37.6
Platelet count x 10^9/uL	155
Absolute neutrophil count x 10^9/uL	12.1
Absolute lymphocyte count x 10^9/uL	20.2
Absolute monocyte count x 10^9/uL	4
Nucleated RBC x 10^9/uL	8

Peripheral blood smear

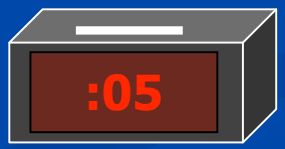


Of the following, the MOST accurate statement regarding the infant's hematologic abnormality is that:

- hyperleukocytosis is an essential diagnostic criterion
- peripheral blood blast counts are usually higher than bone marrow blast counts
- spontaneous resolution rarely occurs
- subsequent development of lymphoblastic leukemia is predicted
- the disorder results from a gene mutation on chromosome 21



Answer Now



Hyperleukocytosis

- Differential diagnosis
    - transient abnormal myelopoiesis
    - congenital leukemia
    - infection
    - leukemoid reaction
- Case Diagnosis: Transient abnormal myelopoiesis
    - Evidence:
        - trisomy 21
        - absence of platelet abnormality (r/o infection, leukemoid reaction)
        - incidence in trisomy 21... TAM (10%) vs congenital leukemia (rare)

Transient Abnormal Myelopoiesis

- synonyms: transient leukemia or transient myeloproliferative disease
- trisomy 21
- presentation variable
  - fetus: hydrops, anemia, tissue infiltration (liver, spleen,skin, heart)
  - neonate: skin infiltrates, exudative effusions (pleural, pericardial, and ascites), respiratory distress, and hepatosplenomegaly
- age at diagnosis (avg): 7 days
- spontaneous resolution: 3 months
- hematologic abnormalities:
  - hyperleukocytosis with blasts in peripheral blood ... diagnostic ...

    TAM originates in fetal liver rather than bone marrow
  - normal Hb and platelet counts
- preleukemic state (acute lymphoblastic > myeloblastic)
  - age at onset (avg) 20 months

A growth-restricted male infant was born by vaginal delivery at 35 weeks' gestation. A sibling died of a similar illness 2 years ago. Liver failure is evident at birth:

- **jaundice absent hepatosplenomegaly**
- **metabolic acidosis**
- **hypoglycemia**
- **mixed hyperbilirubinemia**
- **hypoalbuminemia**
- **coagulalopathy (severe)**

Additional studies:

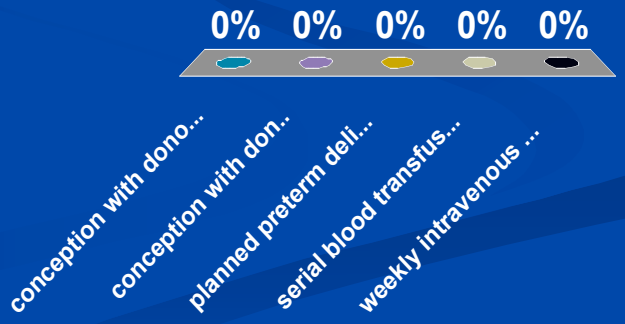
- **elevated [ferritin] and [alpha-fetoprotein]**
- **MRI: consistent with iron deposition in liver, pancreas, thyroid**

Of the following, the MOST likely approach to prevent this disorder from occurring in a future pregnancy is:

- conception with donor egg
- conception with donor sperm
- planned preterm delivery
- serial blood transfusions during pregnancy
- **weekly intravenous immunoglobulin administration during pregnancy**

Answer Now

:05



Causes of Neonatal Liver Failure

Hematologic	**Congenital leukemia** **Hemophagocytic lymphohistiocytosis**	**Hepatic neuroblastoma** **Myelodysplasia**
Infectious	**CMV** **Enterovirus** **Hepatitis A, B, and C virus** **Herpes simplex virus** **Human herpes virus 6**	**Parvovorus B19** **Rubella** **Syphilis** **Toxoplasmosis**
Metabolic	**Alpha-1 antitrypsin deficiency** **5 beta-reductase deficiency** **Galactosemia** **Glycogen storage disease** **Hereditary fructose intolerance**	**Neonatal hemochromatosis** **Niemann-Pick disease type C** **Tyrosinemia** **Zellweger syndrome**
Vascular	**Ischemia** **hemangiomatosis**	
Other	**Mitochondrial cytopathy** **Neonatal lupus erythematosus**	

- **Neonatal hemochromatosis** (NH) is this infant's most likely diagnosis because of the following:
  - fetal onset of liver dysfunction
  - elevated ferritin and alpha-fetoprotein (AFP) concentrations
  - magnetic resonance imaging (MRI) findings showing a dark liver, pancreas, and thyroid gland (iron deposition)
  - Recurrence with non-Mendelian and non-mitochondrial inheritance (80% recurrence):
    - Sporadic occurrence with unaffected offspring before delivering the first infant with this disease
    - A high recurrence rate (up to 80%, independent of sex) with future affected pregnancies leading to either a fetal loss or an ill infant
    - Documented cases of women giving birth to affected infants with different male parentage
    - Lack of affected infants with the same father and different female parentage
    - Consistent with alloimmune disease and transplacental passage of antibodies against an unknown antigen (similar to Rh disease)

Prevention of Neonatal Hemochromatosis

- Weekly intravenous immunoglobulin (IVIG) from 18 weeks' gestation until delivery
- Outcomes:
  - Survival nearly 100% (versus rare)
  - Evidence of fetal disease ...
    - severe symptoms absent ...
    - biochemical findings of NH (elevated serum ferritin and [AFP] in 80%
    - clinical evidence of liver disease ...20% ... most responded to antioxidants
    - liver transplantation ... none

The infant depicted in Figures 1, 2, 3, and 4 was transferred for management of severe respiratory failure. The pregnancy, labor, and delivery were uncomplicated. Antenatal testing and sonography had been declined. The infant died despite intensive medical management. Figure 1: Face and head of the infant in the vignette. Figure 2: Frontal image of the face, head, torso, and extremities of the infant in the vignette.

Figure 1

Figure 2

Figure 3: Right hand and feet of the infant in the vignette.

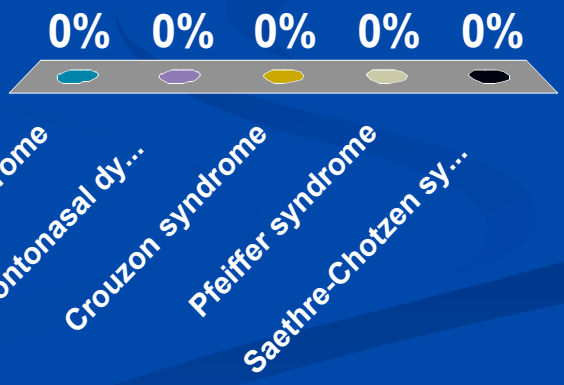
Figure 4: Autopsy of the infant in the vignette showing the intestines and left lobe of the liver herniated into the left chest. The heart is located in the right thorax and lungs are hypoplastic.

Figure 3

Figure 4

Of the following disorders, the MOST likely diagnosis in this infant is :

- Apert syndrome
- craniofrontonasal dysplasia
- Crouzon syndrome
- Pfeiffer syndrome
- Saethre-Chotzen syndrome



Answer Now

Apert syndrome

- Distinguishing features:
  - Symmetric polysyndactyly of the hands (mitten hands) and feet (sock toes)
  - Brachyturricephaly (towering head), large anterior and posterior fontanels, a wide sagittal suture, and megencephaly
  - diaphragmatic hernia (other anomalies more frequently found than in other craniosynostosis syndromes)
- Common to Pfeiffer and Crouzon syndromes: brachiturricephaly, exorbitism, maxillary hypoplasia, and mandibular prognathism
- Older paternal age
- Sporadic, occasionally autosomal dominant
- fibroblast growth factor receptor 2 gene located on chromosome 10q25-q26

A 29 year old woman at 31 weeks' gestation :

- nausea
- vomiting
- right upper quadrant pain
- jaundice
- obtundation
- hypertension

Laboratory studies:

- thrombocytopenia (platelet count 85,000/mm^3)
- elevated serum transaminases
- hyperammonia
- prolonged prothrombin time
- hypoglycemia
- Viral causes for liver dysfunction … excluded

Liver biopsy … microvesicular fatty infiltration

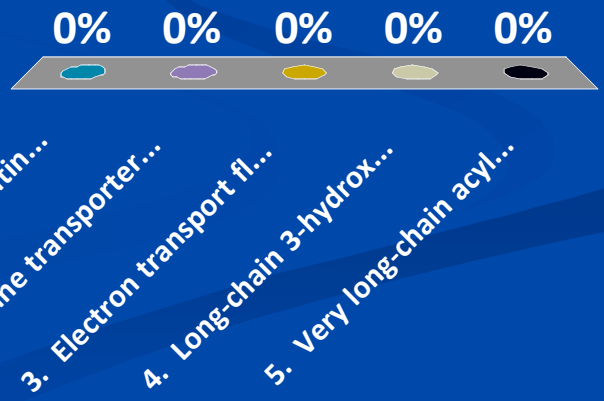
Family History: sibling died of SIDS

Of the following, the MOST likely diagnosis for the fetus is:

1. Carnitine-acylcarnitine translocase deficiency
2. Carnitine transporter deficiency
3. Electron transport flavoprotein-alpha deficiency
4. Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency
5. Very long-chain acyl CoA dehydrogenase deficiency

Answer Now

:10



Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency

- Acute Fatty Liver of Pregnancy
  - 1 in 5 chance of delivering an infant with LCHAD
  - 1 per 13,000 deliveries, usually 30 - 38 weeks' gestation
  - No ethnic or pregnancy features prevalent
  - recurrence possible
  - jaundice, hypoglycemia and elevated PT … differentiates from HELLP syn
  - Recovery … after delivery of the fetus
  - About 60% of mothers carrying fetuses with LCHAD deficiency develop AFLP, HELLP syndrome, or preeclampsia.
  - G1528C mutation (homozygous or compound heterozygote) predisposes mother to AFLP

- Fatty acid oxidation disorders
  - common causes of severe metabolic disease
  - 1:8000 to1:100,000 individuals
  - AR
  - Fatty acids …largest energy reserve
  - FA oxidation …
    - important during fasting and stress
    - primary source of energy … heart, liver, and skeletal muscles

Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency

- Presentation within hours to months after birth
  - prematurity
  - IUGR
  - nonketotic hypoglycemia,
  - metabolic acidosis
  - hyperammonemia
  - hypotonia
  - hepatic encephalopathy
- Early or late presentation :
  - coma
  - cardiomyopathy
  - peripheral neuropathy
  - skeletal myopathy
  - retinopathy
  - sudden unexpected death (5% - 8% of SIDS cases)
- Late presentation:
  - episodic symptoms …myopathy, neuropathy, and retinopathy
- Laboratory:
  - normal to decreased free carnitine,
  - increased acyl-to-free carnitine,
  - increased free fatty acids,
  - increased C_{16}-OH and C_{18}-OH carnitines
- Mass tandem mass spectrometry … identify LCHAD

Figure 1. Proposed Mechanism for Fatty Liver of Pregnancy, HELLP Syndrome, and Preeclampsia

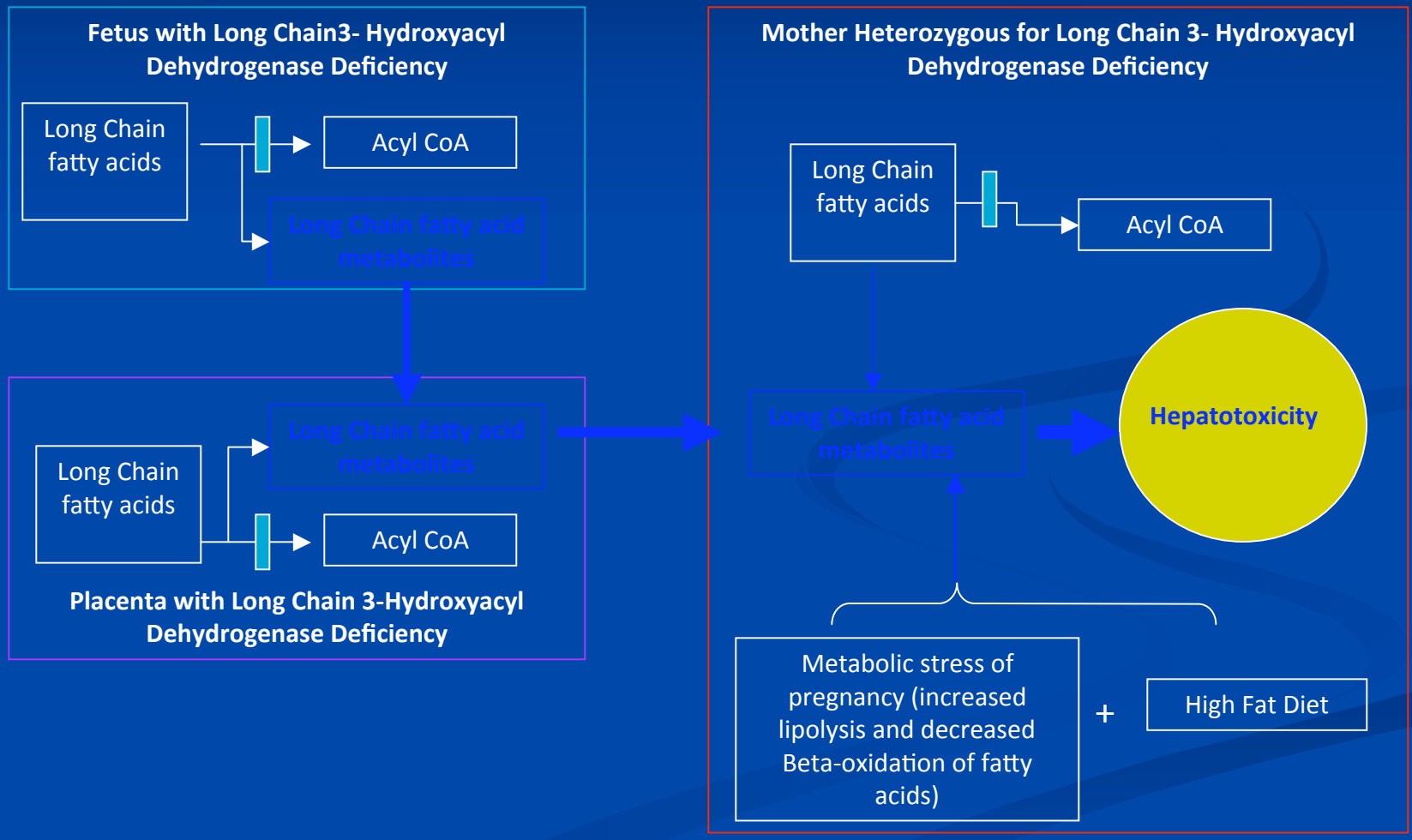
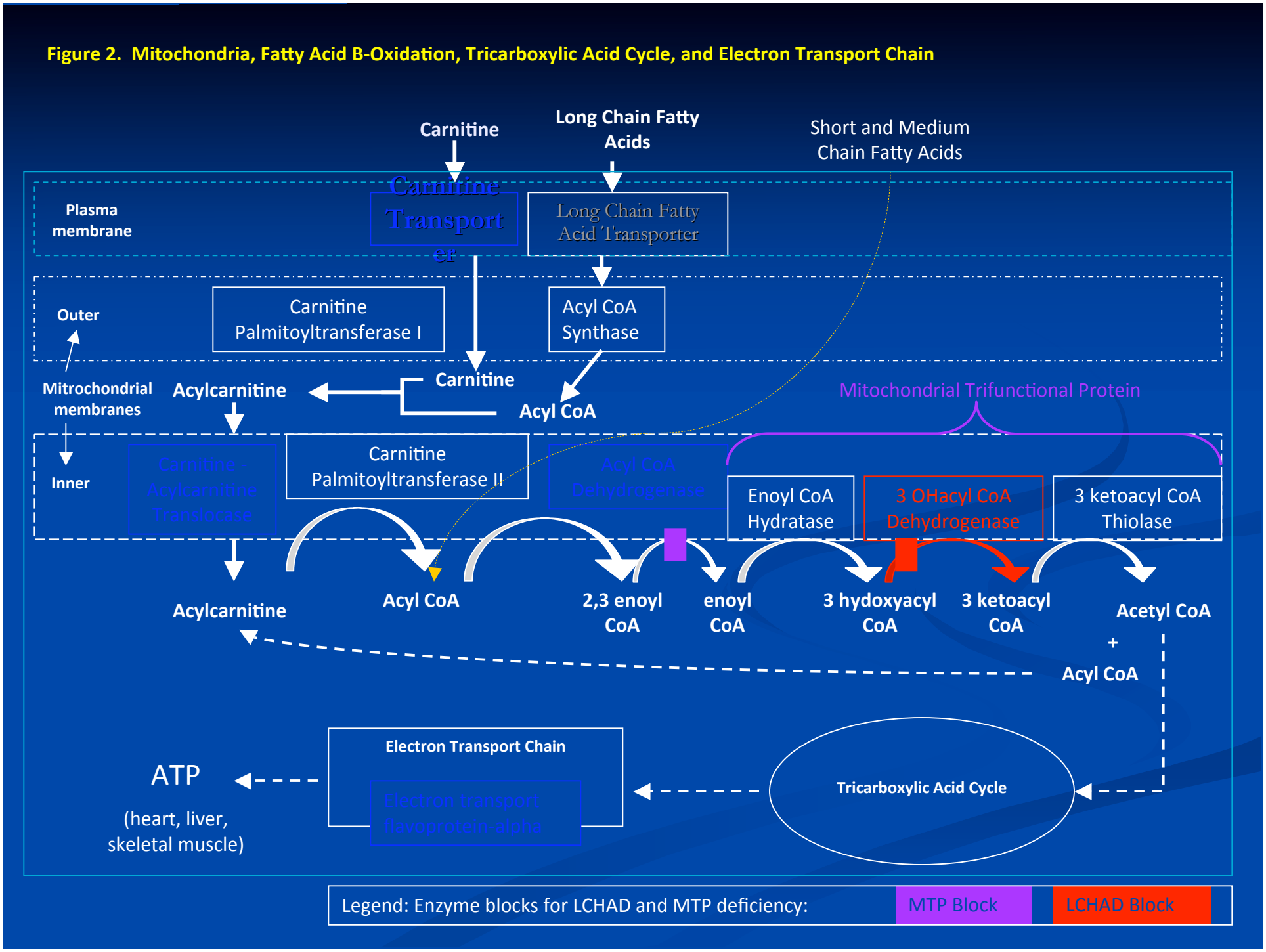
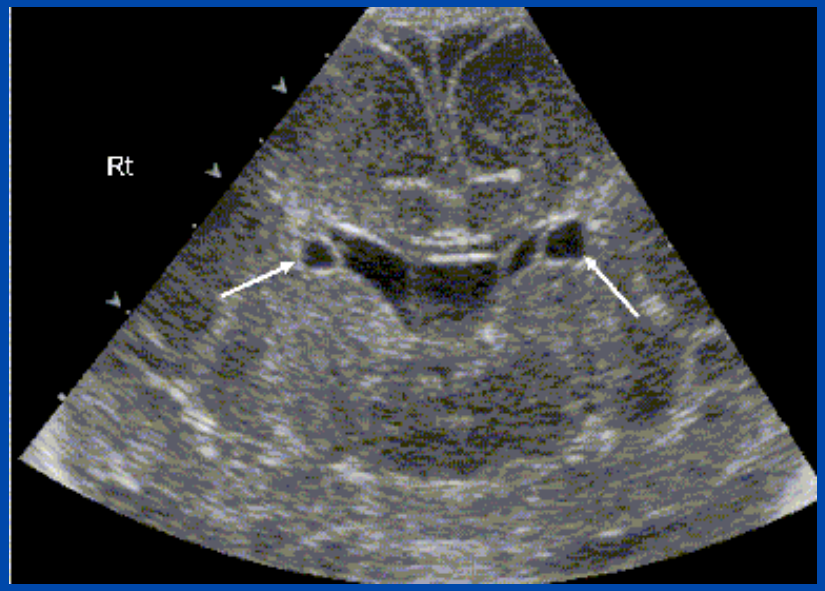


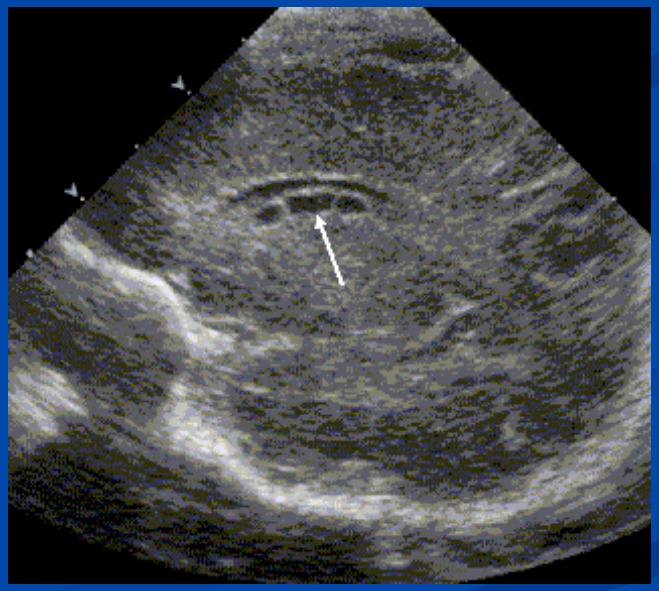
Figure 2. Mitochondria, Fatty Acid B-Oxidation, Tricarboxylic Acid Cycle, and Electron Transport Chain



A 14 day old former 27 weeks' gestation male is recovering from RDS and hypotension.

HUS reveals cystic changes (Figure 1 and Figure 2).



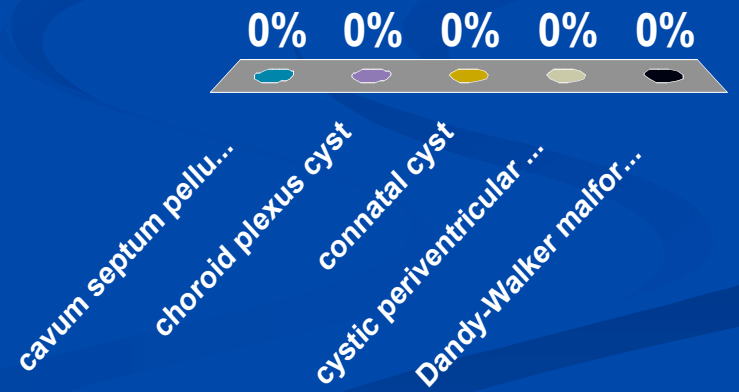


Of the following, the HUS features of the cysts indicated by the arrows in this infant are MOST consistent with the diagnosis of:

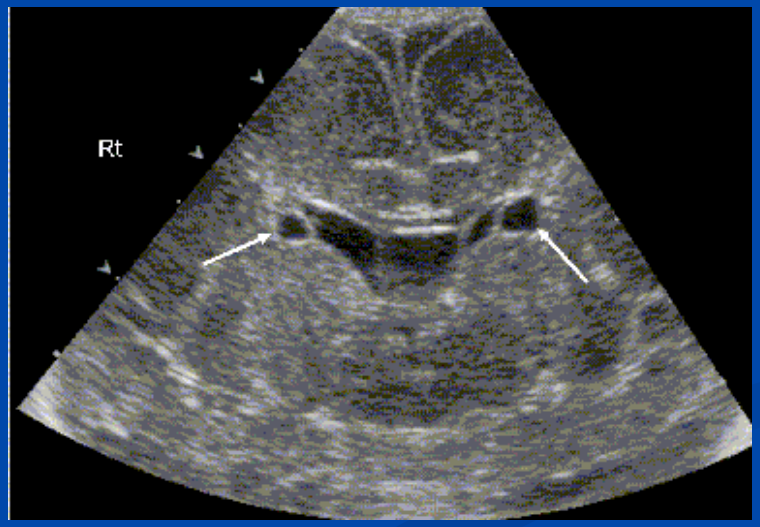
1. cavum septum pellucidum
2. choroid plexus cyst
3. connatal cyst
4. cystic periventricular leukomalacia
5. Dandy-Walker malformation

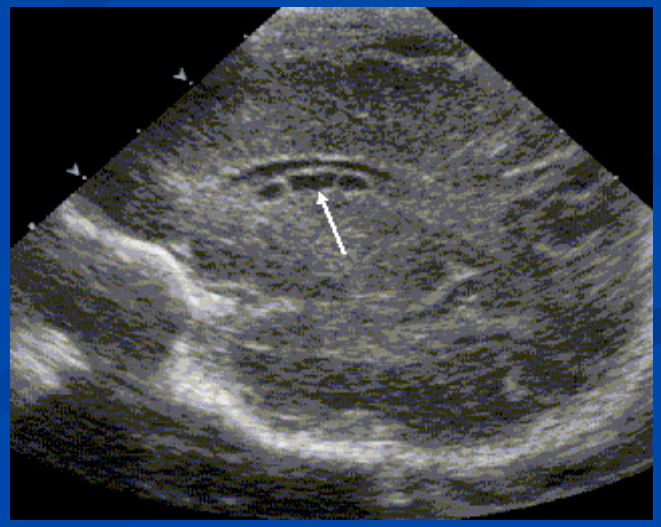
Answer Now

:05

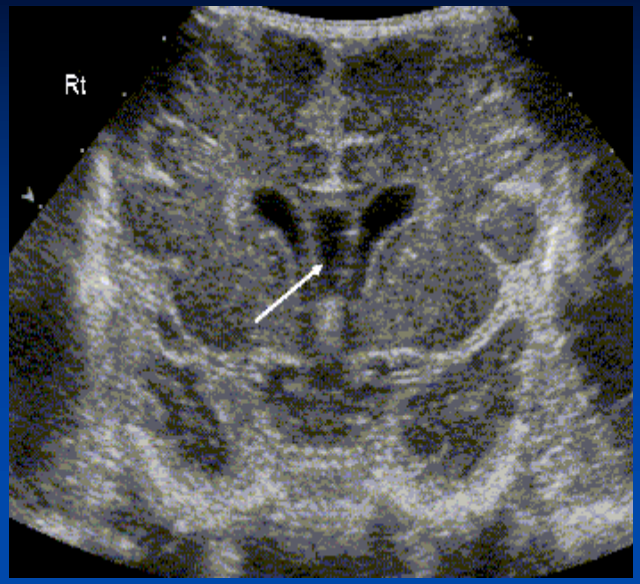


- **Connatal cysts (or frontal horn cysts)**
  - location: at or just below the superolateral angles of the frontal horns of the lateral ventricles, mostly anterior to the foramina of Monroe
  - normal variants caused by close approximation of the walls of the frontal horns of the lateral ventricles proximal to their external angles
  - rounded configuration and vary in size in millimeters
  - incidence of connatal cysts is 0.7% in preterm low-birthweight infants
  - benign and resolve spontaneously

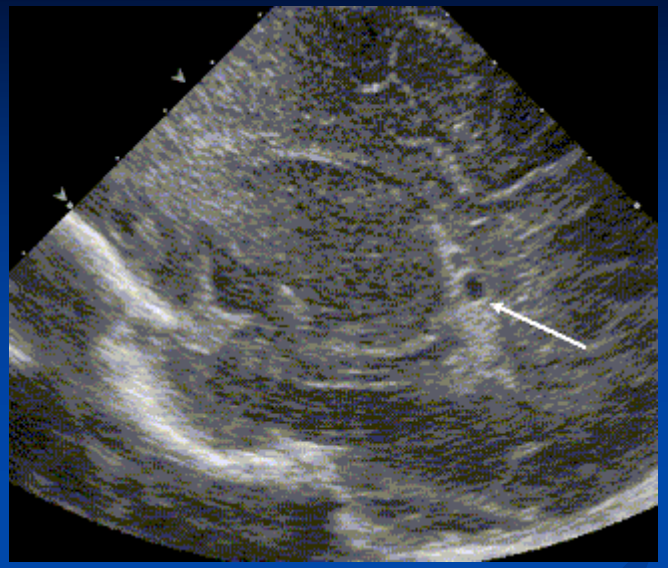




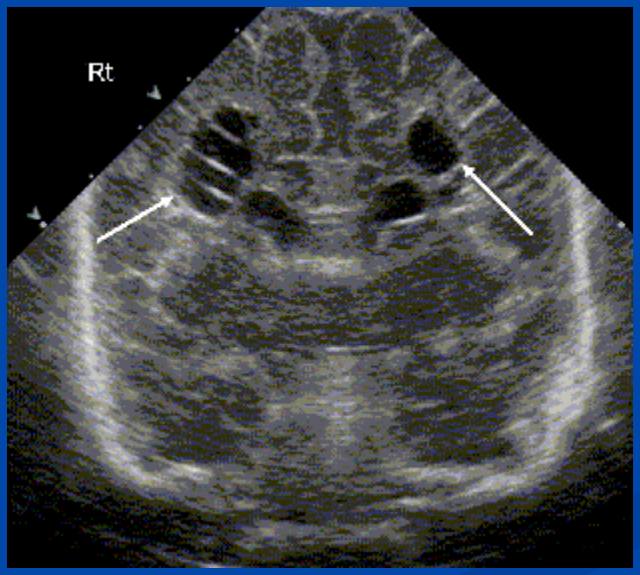
Cavum septum pellucidum



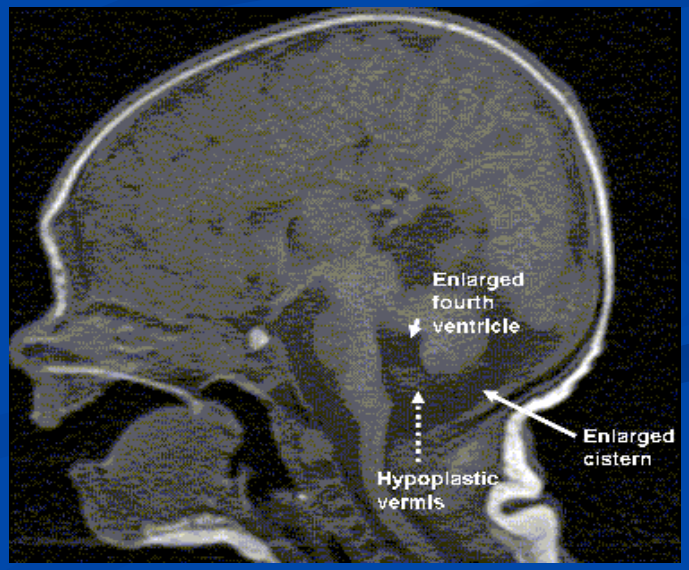
Choroid plexus cyst



Periventricular leukomalacia



Dandy-Walker malformation



Participant Scores

1049.4	Participant 236
824.55	Participant 76
809.09	Participant 161
766.22	Participant 70
754.48	Participant 170

A 33-year-old woman developed a flulike illness before the beginning of the third week after conception.

- History:

  care of a friend's stray cat with kittens about a week before the onset of illness

- Laboratory:

  tested for toxoplasmosis, confirming acute infection

- Treatment:

  pyrimethamine and sulfadiazole along with leucovorin supplements

- Prognosis:

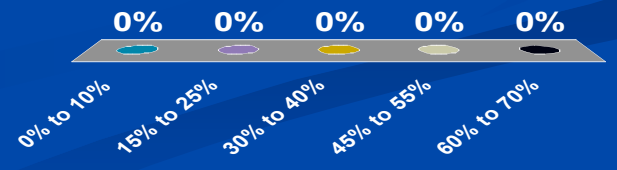
  estimate the risk of infection to her fetus

Of the following, fetal risk following maternal toxoplasmosis infection acquired near the beginning of the first trimester is

- 0% to 10%
- 15% to 25%
- 30% to 40%
- 45% to 55%
- 60% to 70%

Answer Now

:10



Toxoplasmosis

- kittens are more likely to excrete *Toxoplasma* oocysts than are adult animals
- Congenital infection:
  - 1/1000 to 1/10000 LB in USA
  - most cases of (70%-90%) are asymptomatic at birth
    - some → visual difficulties, learning problems, or mental retardation months to years later
  - Some have systemic disease in neonatal period

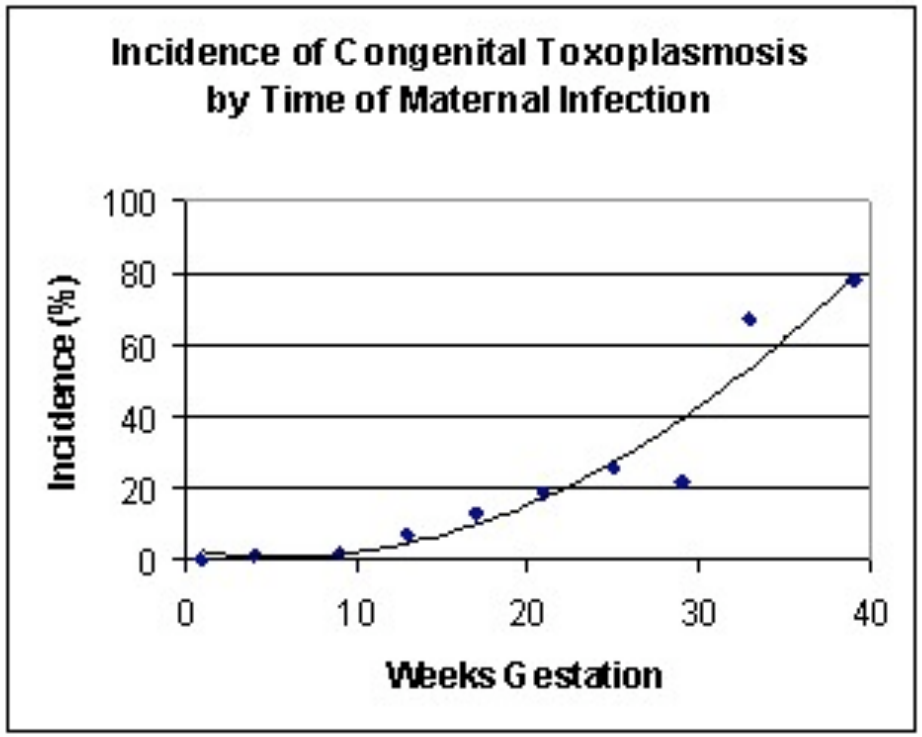
Neonatal toxoplasmosis

- systemic presentation at birth
  - maculopapular rash, lymphadenopathy, hepatosplenomegaly, thrombocytopenia, jaundice
  - central nervous system
    - meningoencephalitis, intracranial calcifications, hydrocephalus, microcephaly, chorioretinitis, seizures,

      deafness
- infection also can be fatal before or shortly after birth

Maternal toxoplasmosis: fetal risk

- general rule:
  the later in pregnancy the primary infection occurs,
  the higher the rate of transmission

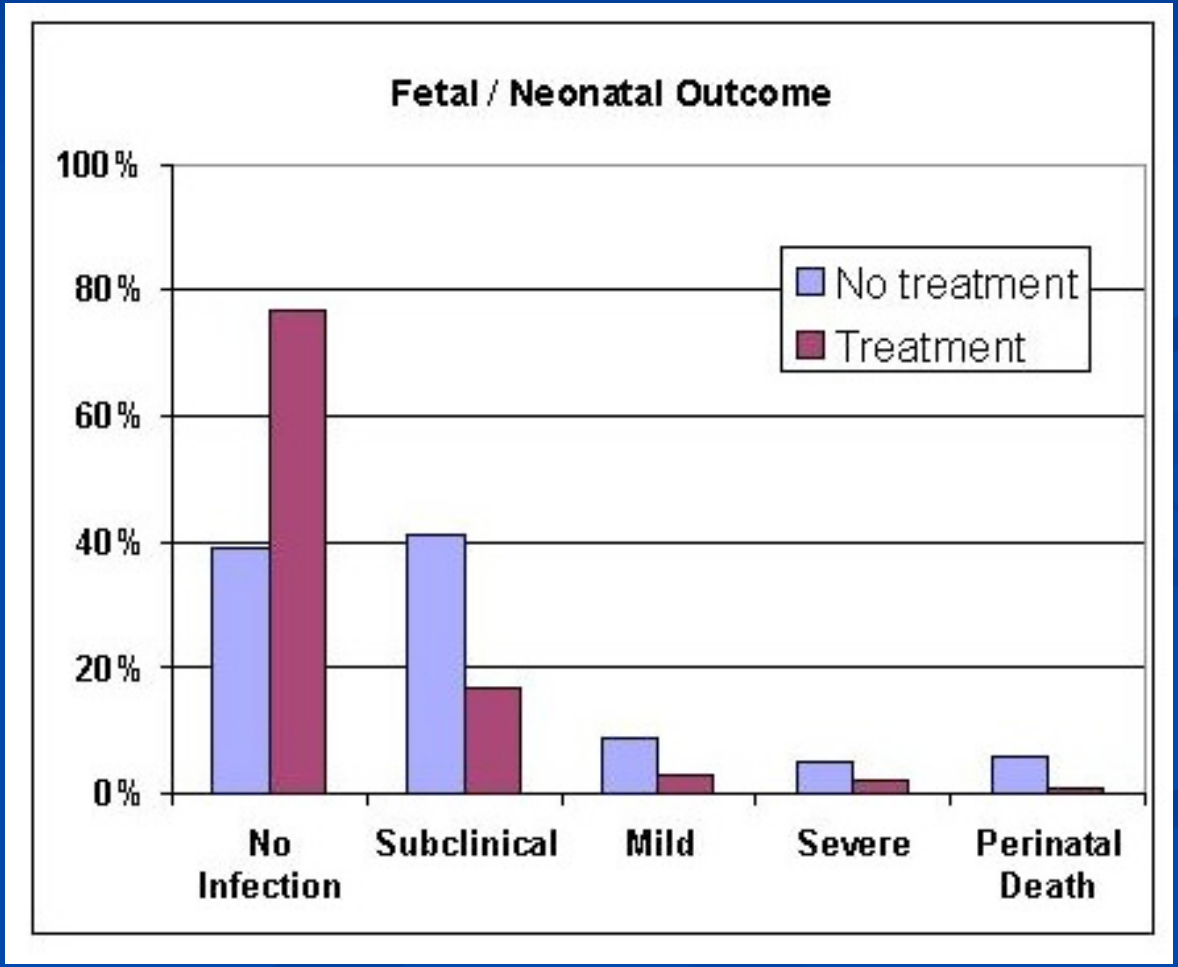


*Adapted from Hohlfeld and colleagues (1994).

Toxoplasmosis: fetal risk & GA

- highest risk for adverse fetal outcome is when the pregnant woman becomes infected during the 10th to 24th week of gestation
  - during that period the chance of transmission is moderate (approximately 4%-24%)
  - but, severity tends to be the highest
- >24th week :
  - incidence of infection continues to rise
  - infections tend to be subclinical

Treatment of the infected pregnant woman can reduce the incidence and severity of fetal and congenital toxoplasmosis



A 4-hour-old preterm male infant was delivered at 32 weeks' gestation

- birthweight 1,500 g
- rupture of membranes at time of delivery
- negative maternal rapid plasma reagin, human immunodeficiency virus, group B *Streptococcus*, and hepatitis B surface antigen
- infant is hemodynamically stable and does not require any respiratory support

Of the following, the MOST appropriate time to administer hepatitis B vaccine to this 32 wk, 1500 g infant is: [Maternal HbsAg (-)]

0% 1. at 2 months' chronologic age

0% 2. at 40 weeks' postmenstrual age

0% 3. when the weight is 2,000 g or more

0% 4. within 12 hours of birth

0% 5. within the first 30 days after birth

Answer Now

10

Perinatal Transmission of HBV: factors

- Blood exposure during labor and delivery
- Antigen(s) present:
  - 70% to 90% for infants born to mothers positive for hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg)
  - 5% to 20% for infants born to HBeAg-negative mothers

Hepatitis B Virus: transmission

- in utero transmission of HBV
  <2% of perinatal infections

- breastfeeding by an HBsAg-positive mother
  does not increase the infant's risk of acquiring HBV infection

Hepatitis B Virus: Vaccine-1

- **Birth Dose of Hepatitis B Vaccine**
  - to prevent perinatal infection among infants born to HBsAg-positive mothers who are not identified because of errors in maternal HBsAg testing or reporting of test results
  - should be administered as part of the routine care of all *medically stable infants weighing 2,000 g or more at birth* born to HBsAg-negative mothers

Hepatitis B Virus: Vaccine-2

- by the chronologic age of 1 month, all medically stable preterm infants, regardless of initial birthweight or gestational age, are as likely to respond to hepatitis B immunization as are older and larger infants…GIVE Hepatitis B vaccine dose 1-30 days of chronologic age if medically stable, or at hospital discharge if before 30 days of chronologic age
- the first HBV dose needs to be administered within 12 hours of birth along with hepatitis B immune globulin when the mother's HBsAg status is positive or unknown

15-day-old, 28 weeks' gestation male infant developed several painful red macules and a hemorrhagic bulla on his right thigh

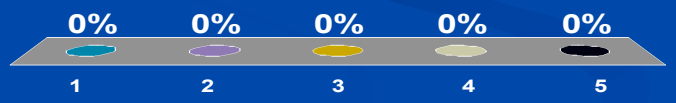
- macules 1.5 to 3.0 cm in diameter
- Within 12 hours, the macules vesiculated, some with hemorrhage, and ulcerated.

Painful red macules→

- ulcers developed a necrotic, black, depressed appearance and centers became encrusted
- biopsy of the ulcer …vasculitis with few inflammatory cells
- edema, hemorrhage, and necrosis were found surrounding the veins and some arteries
- bacteria were seen in the perivascular tissue and vessel walls.
- infant developed shock

Of the following, the organism MOST often associated with the skin lesions described for this infant is:

1. *Candida albicans*
2. *Pseudomonas aeruginosa*
3. *Staphylococcus aureus*
4. *Streptococcus agalactiae*
5. *Treponema pallidum*



Answer Now

Ecthyma gangrenosum

- Occurs in 2 - 6% of all infections caused by *Pseudomonas aeruginosa*
- Other organisms: less frequent association
  - group B streptococcus
  - *Aeromonas hydrophilia*,
  - *Enterobacter* species, *Escherichia coli*, *Proteus* species, *Pseudomonas cepacia*, *Serratia marcescens*,
  - *Xanthomonas maltophilia*, *Aspergillus* species, mucorales, and *Candida albicans*

Ecthyma gangrenosum: clinical signs

- begins as a painful red or purpuric macule that centrally vesiculates or becomes pustular ± bullae
- lesion quickly ulcerates and becomes necrotic in the center
- black, crusted eschar covers an erythematous base …microscopically …a vasculitis especially the veins
- caused by
  - enzymes, proteases (elastase, gelatinase, collagenase, lecithinase)
  - endotoxin
  - exotoxins A and S

Ecthyma gangrenosum: lesions

- lesions are characteristically devoid of inflammatory cells
- culture of the base of these lesions, not the exudate or eschar, to determine the microbial source of infection
- presence of ecthyma gangrenosum generally indicates treatment with anti-*Pseudomonas* antibiotic agents

A term infant with apparent clitoromegaly and posterior labial fusion, with palpable masses in the labial folds

amniocentesis

- karyotype of 46,XY

- pelvic US:
  - Descended bilateral testes
  - Intact bilateral male tubular elements (epididymis, vas deferens, and seminal vesicles)
  - No uterus or fallopian tubes

The findings in this infant with ambiguous genitalia suggest:

0%	1.	deficiency in müllerian inhibiting substance
0%	2.	5 alpha-reductase deficiency
0%	3.	placental aromatase deficiency
0%	4.	testicular feminization syndrome
0%	5.	Yp deletion with loss of the SRY gene

Answer Now

10

5 α-reductase deficiency

- Key characteristics:
  - Appropriate internal structures because testosterone is produced at normal levels by the testes and acts locally to develop wolffian structures
  - Testosterone is not converted in peripheral tissues to DHT resulting in undervirilization of external genitalia, varies from apparent clitoromegaly, urogenital sinus, posterior labial fusion, hypospadias, or a micropenis

SRY gene on Y chromosome

- Presence of Y (SRY) gene → undifferentiated gonad becomes a testis
  - testosterone (produced by the testes)
- ↓ 5 α-reductase converts T → DHT
  - stronger androgen dihydrotestosterone (DHT)
  - masculinization of external genital structures
- Absence of the SRY gene, the gonads become ovaries

Muellerian inhibition

- normal male karyotype and the presence of testes rules out an absence of the SRY gene
- absence of müllerian structures, such as the uterus, suggests adequate production of MIS from testicular Sertoli cells
- Leydig cell testosterone production is supported by the presence of male tubular structures.

Androgen insensitivity syndrome

- testicular feminization …androgen insensitivity syndrome (AIS)
- peripheral androgen receptor or postreceptor defects → lack of androgenic stimulation
- complete AIS …wolffian ducts fail to develop & external genitalia are female-appearing
  - in contrast to the infant in the vignette
- partial AIS or incomplete testicular feminization
  - →incomplete masculinization of the external genitalia
  - impaired wolffian duct development

Placental aromatase

- placental aromatase deficiency
  - female fetus and mother are virilized
  - diminished placental conversion (aromatization) of fetal androgens to estrogens …increase in circulating androgens
  - Patient in this case a genetic male

A female born at ~33 weeks GA has a sonorous seal-bark cry in the delivery room

- Prenatal:
  US- absent fetal stomach bubble
  Polyhydramnios
- Neonatal:
  Excess salivation
- PE:
  no dysmorphic features, mild respiratory distress, abdomen flat, no other abnormal findings
- Stabilization:
  - orogastric tube is inserted to 9 cm at the infant's lower alveolar ridge

Of the following, the MOST important study to complete before operative repair in this infant is:

1. chromosomal analysis
2. cranial ultrasonogram
3. echocardiogram
4. renal ultrasonogram
5. skeletal survey

Answer Now

Esophageal Atresia (EA): Dx

- Prenatal ultrasonogram >18th week of gestation fails to identify the fetal stomach bubble
  - absent fetal stomach bubble and polyhydramnios has a positive predictive value of 56% for EA
- Presentation
  - sonorous seal-bark cry …associated tracheomalacia
  - excessive oral secretions first few hours after birth

Esophageal Atresia (EA)

- Associated anomalies: 60% overall
  - cardiac (25%),
  - genitourinary (15%),
  - skeletal (14%), and
  - intestinal atresias (13%)
- VACTERL association

  (vertebral defects, anorectal abnormalities, cardiac defects, TEF, renal abnormalities, limb defects)

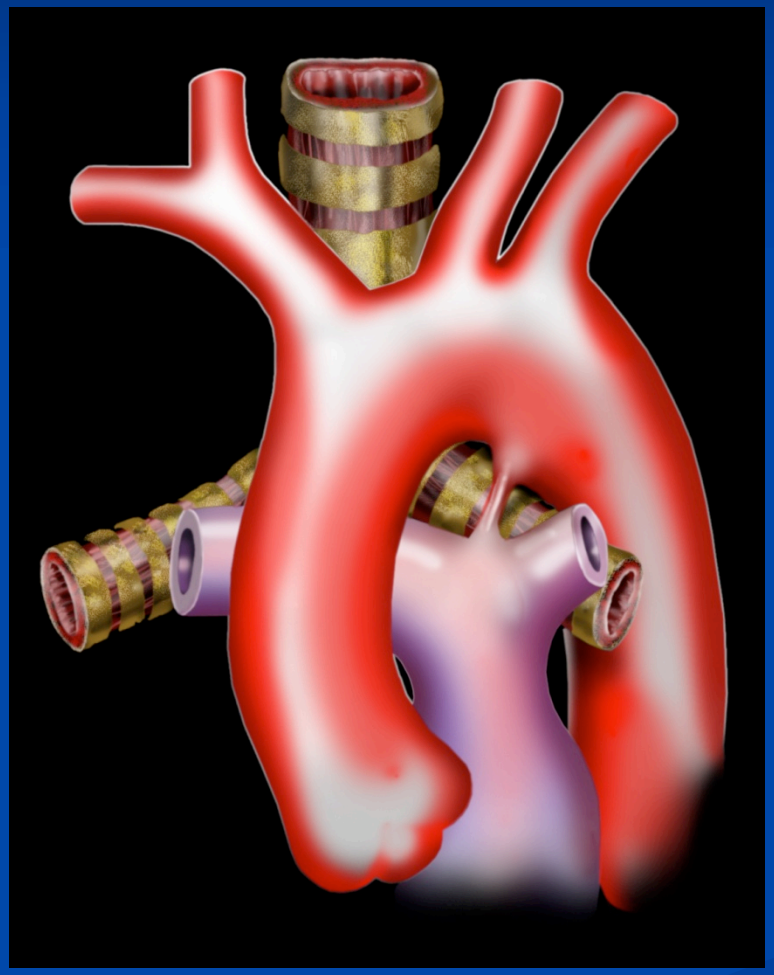
  ~10% to 25% of cases

EA: what matters pre-op??

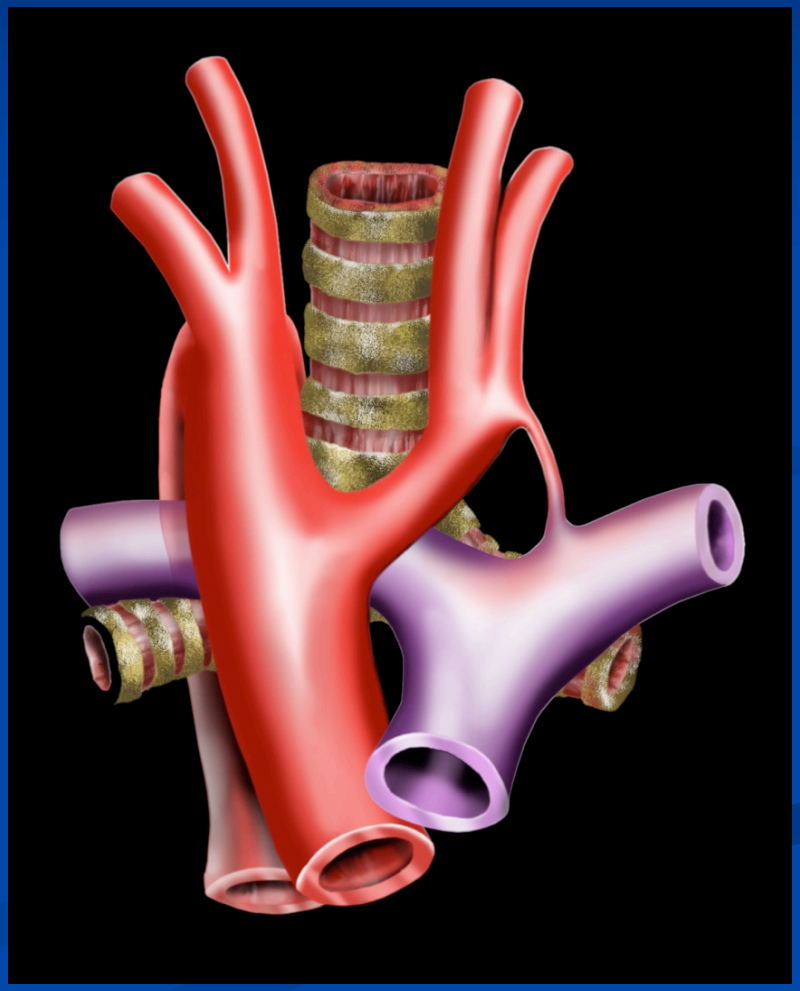
- Cardiovascular anomalies: ~25% of infants with EA have associated
  - ventricular septal defect
  - tetralogy of Fallot
- Newborns with EA should undergo echocardiogram before operative repair
  - position of the aortic arch
  - identify potential structural abnormalities

Aortic arch positioning:

- Left sided



- Right sided (2-3% of EA)



EA: other studies

- Chromosomes: with no dysmorphic features, chromosomal analysis is not necessary before operative repair;
  - EA and TEF ~normal chromosomes
  - EA … trisomy 21 and 18, and 13q deletion

- CNS abnormalities rare with EA …preoperative cranial ultrasonogram not needed in an infant with no dysmorphic features

EA: other studies

- Genitourinary: ~15% of infants with EA have genitourinary anomalies
  - renal ultrasonogram should be done to identify these anomalies
  - not necessary to perform preoperatively
- Vertebro-skeletal: ~14% of infants with EA have vertebral/skeletal abnormalities
  - many vertebral anomalies can be identified by CXR
  - skeletal survey if desired, is not necessary before operative repair

Participant Scores

1349.4	Participant 236
1023.75	Participant 144
1009.09	Participant 161
962.03	Participant 148
960.89	Participant 45

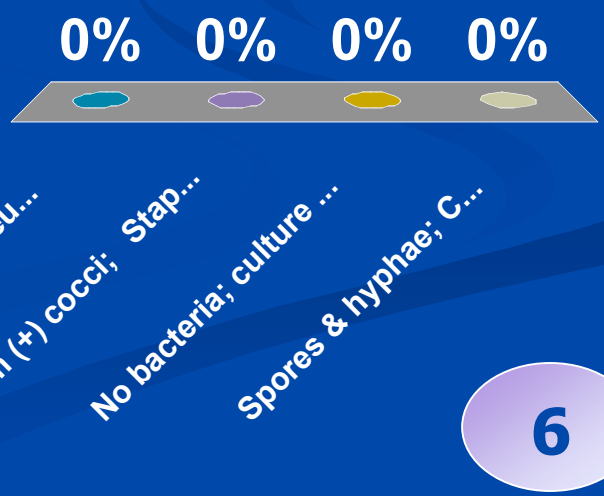
Team Scores

504.85	Other physician
497.95	Medical student
486.88	Pediatrician
486.21	Advance practice nurse
472.95	NPM fellow

One week old. Sick. Skin rash with bullae.
Bullus: broken in process of culture & gram stain.

One week old infant presents with irritability, red rash around neck & skin folds. Skin separation occurs & child cries when shirt is being removed. Some bullae are seen. Gram stain & culture of bullous fluid & base:

1. Gram (-) rods; Pseudomonas
2. Gram (+) cocci; Staphylococci
3. No bacteria; culture negative
4. Spores & hyphae; Candida

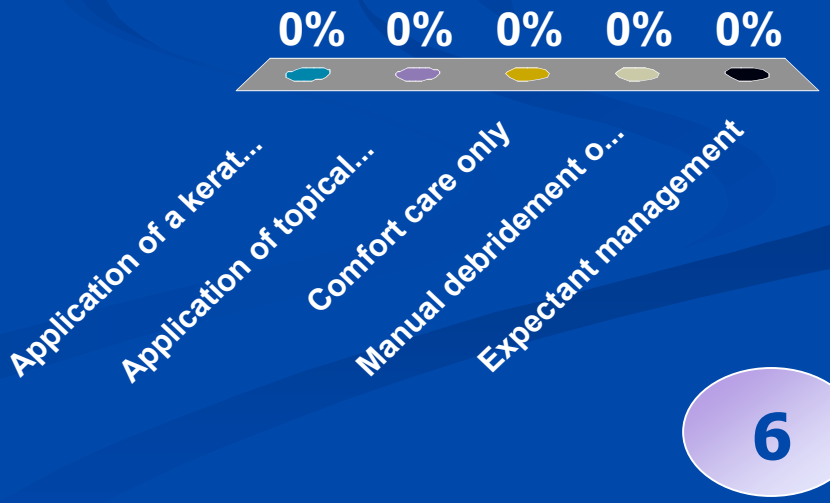


Staphylococcal Scalded Skin Syndrome

- Exotoxin producing *staph aureus*
- Presents with fever, irritability, tenderness
- Epidermolytic toxin
  - Lesions: bullous fluid is sterile
- Culture positive at site of infection (eg, circumcision), blood, CSF.
- Rx: antibiotics & supportive care

An infant is born at 35 weeks' gestation (Figure). Of the following, the initial management of this infant should include which one of the following?

1. Application of a keratolytic agent
2. Application of topical emollients
3. Comfort care only
4. Manual debridement of the membrane
5. Expectant management



Collodion baby: Characteristics

At birth:

- **oiled-parchment-like membrane of thick hyperkeratotic epidermis with underlying yellow, erythematous skin**
- **taut facial skin**
  - **everts the eyelids (ectropion)**
  - **fixates the lip in an O-shape or fish-mouth configuration (eclabium)**
  - **nose flattened**
  - **pinnae malformed**
- **hair absent or perforates the membrane**

Collodion baby: Disorders

- phenotype common to several disorders of cornification:
  - classic lamellar ichthyosis or nonbullous congenital ichthyosiform erythroderma
    - ~ 2/3 of cases
  - less common:
    - autosomal dominant lamellar ichthyosis
    - Trichothiodystrophy
    - recessive X-linked ichthyosis
    - neonatal Gaucher's disease
    - neutral lipid storage disease
    - Sjögren-Larsson syndrome

Collodion baby: Natural History, Rx, M&M

Membrane sheds over months and long-term appearance develops

~ skin biopsy to establish diagnosis at this time

Emollients aids healing, in temperature control, and in control of fluid loss

~ debridement and karytolytics not indicated

> infection and fluid imbalance risks

Mortality with most causes infrequent

Morbidity high:

> chronic barrier dysfunction

> fluid imbalance

> temperature instability

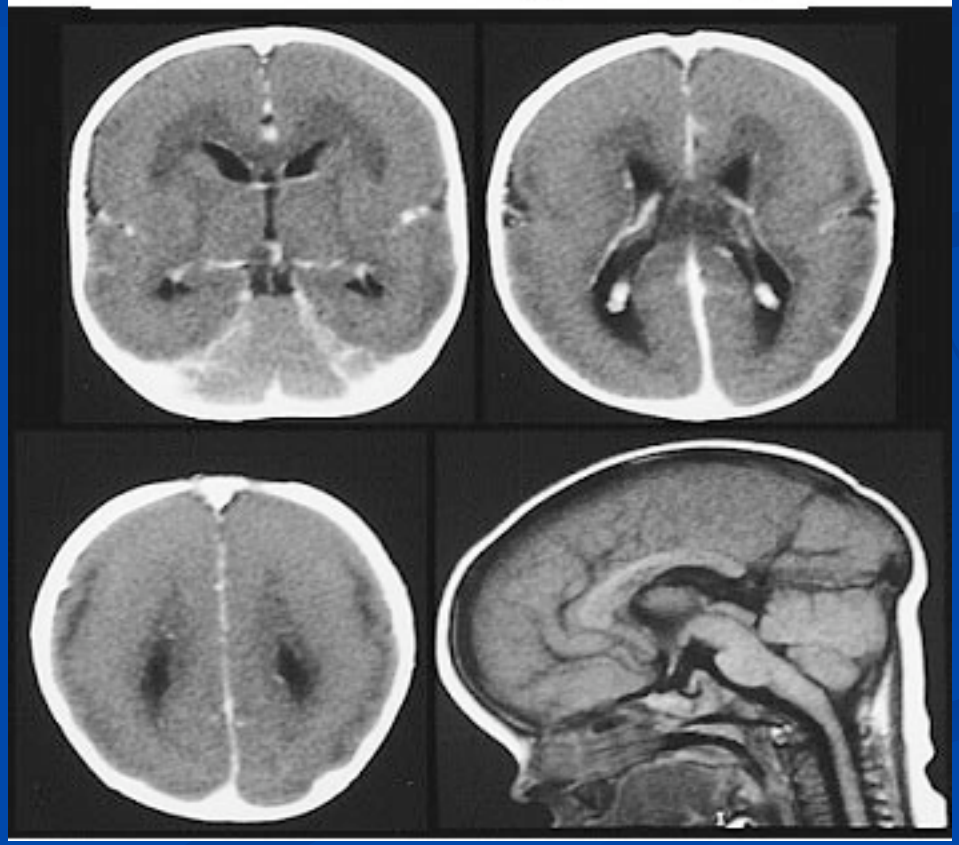
> infection

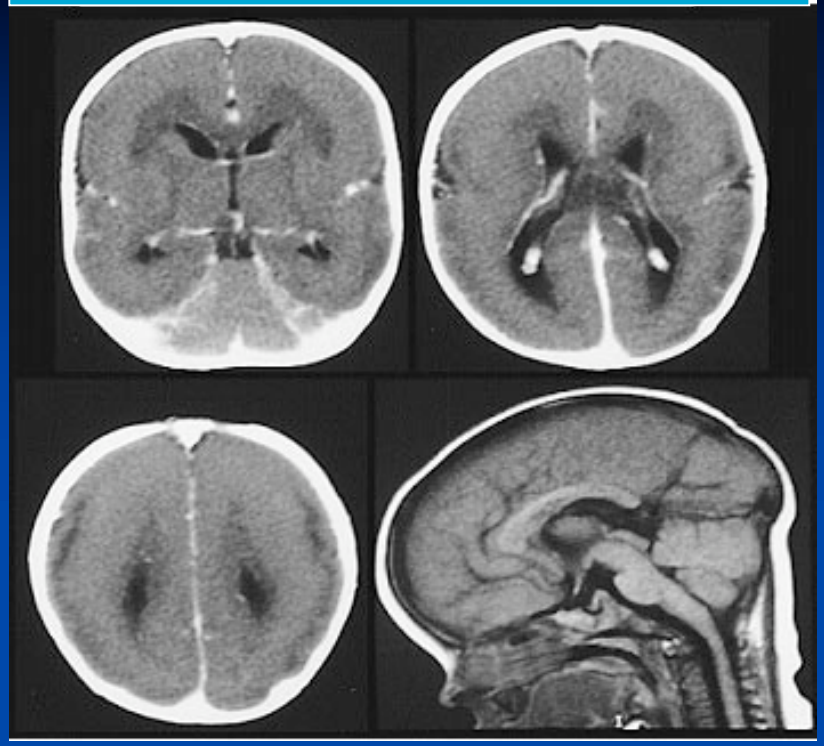
> pain (may require narcotics)

NR+1/07(3)

Child delivered at term, appeared normal, went home with mother. Pediatrician asks you to evaluate the baby one month later because of slow head growth, hypotonia, & paucity of spontaneous movements.

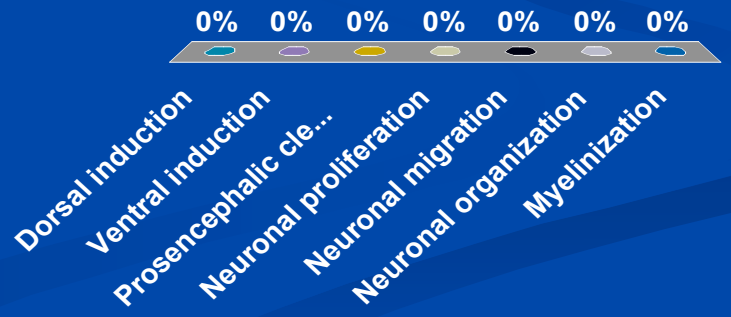
MRI Examination





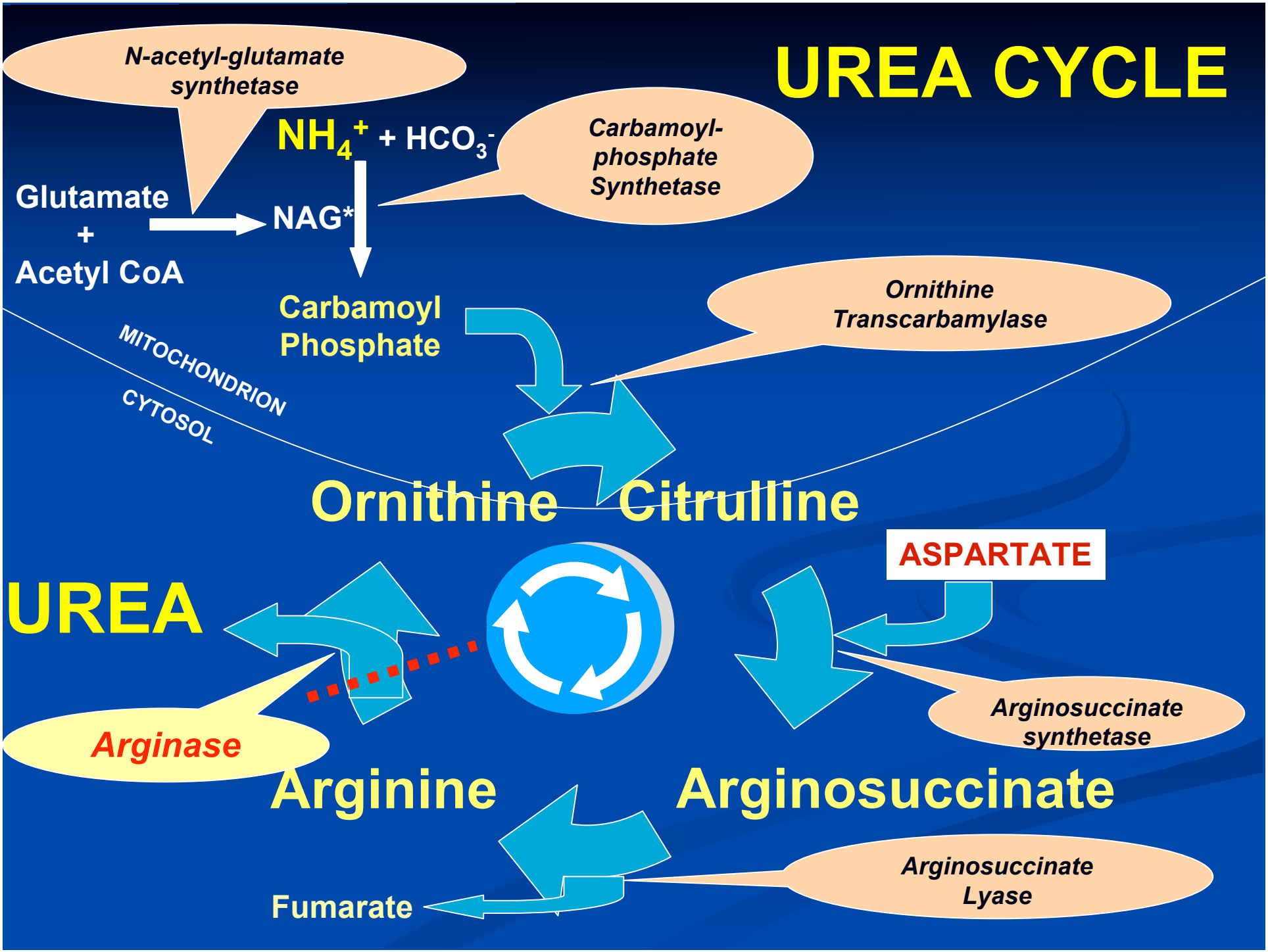
This child's condition resulted from a defect in which of the successive stages of neuronal development?

1. Dorsal induction
2. Ventral induction
3. Prosencephalic cleavage
4. Neuronal proliferation
5. Neuronal migration
6. Neuronal organization
7. Myelinization



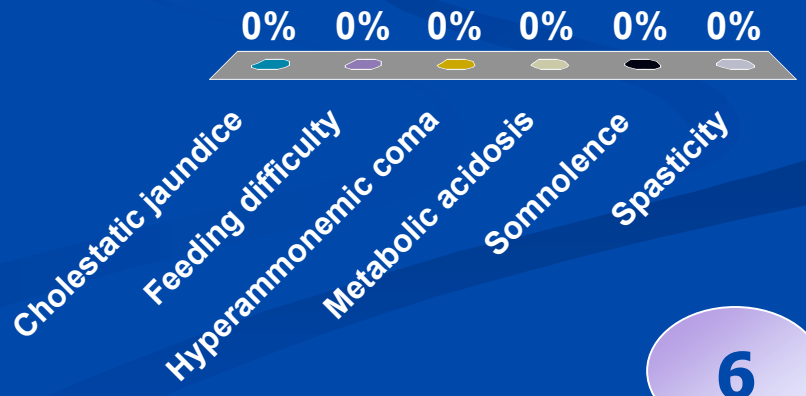
Neuronal development

Stage	Process	Condition
Dorsal induction	Neural plate forms, becomes neural tube	Anencephaly Encephalocele Myelomeningocele
Ventral induction	Prosencephalic development & cleavage	Holoprosencephaly
Neuronal proliferation		
Neuronal migration	**Neurons migrate from subventricular origins to neocortex**	**Lissencephaly**
Neuronal organization	Neurons grow, differentiate, integrate into circuitry	
Myelinization	Oligodendroglia proliferate & differentiate, lead to myelinization	
		NR+7/04(2)


UREA CYCLE
N-acetyl-glutamate synthetase
NH4+ + HCO3-
Carbamoyl-phosphate Synthetase
Glutamate
+
Acetyl CoA
NAG*
Carbamoyl Phosphate
Ornithine Transcarbamylase
MITOCHONDRION
CYTOSOL
Ornithine
Citrulline
ASPARTATE
UREA
Arginase
Arginosuccinate synthetase
Arginine
Arginosuccinate
Arginosuccinate Lyase
Fumarate

ARGINASE DEFICIENCY: Presenting CLINICAL Features?

1. Cholestatic jaundice
2. Feeding difficulty
3. Hyperammonemic coma
4. Metabolic acidosis
5. Somnolence
6. Spasticity



Arginase-1 deficiency

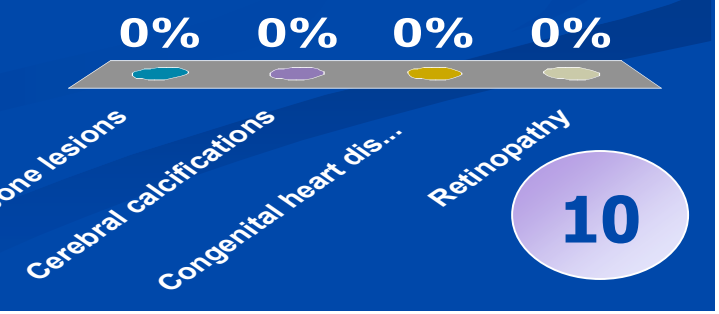
- Rarely presents as hyperammonemic coma
- Neonatal findings:
  - Feeding difficulty
  - Post-prandial irritability (esp. after protein)
  - Somnolence
- Later findings
  - Developmental Delay
  - Spastic Cerebral palsy
- Autosomal recessive
- Diagnosis
  - *Arginase-1* assay (erythrocytes easiest; leukocytes or liver biopsy. Not in cultured fibroblasts)
  - Urine & serum analyses not reliable
- ARG1 gene: 6q23
- State TMS screening
- Rx begun early→nl G&D
- Refer to Center with experience!

NR+10/07(5)

On newborn examination, A baby has this rash and this eye finding.

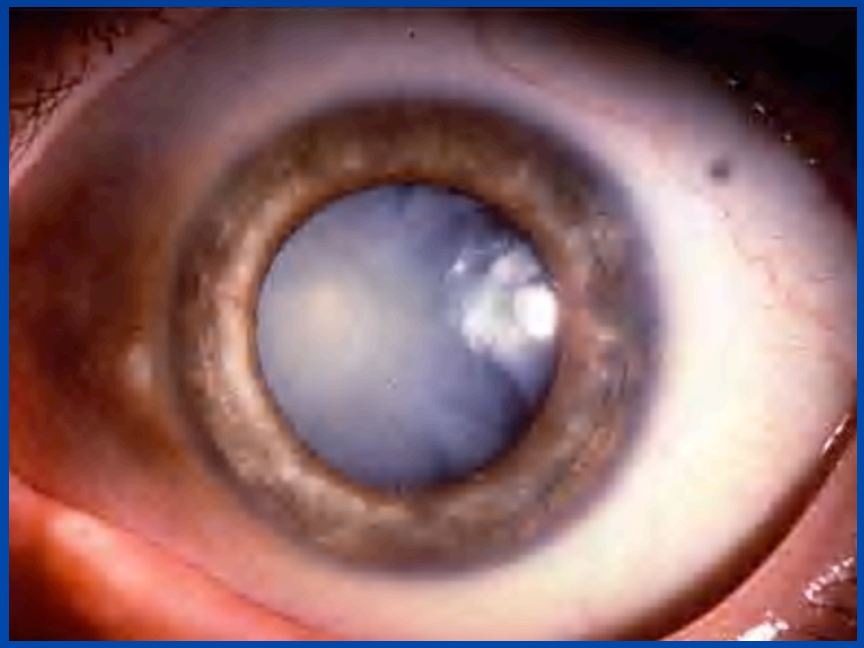
He also has ~75% risk for

1. Bone lesions
2. Cerebral calcifications
3. Congenital heart disease
4. Retinopathy



Blueberry muffin rash of Congenital Rubella

Ophthalmology & Congenital Rubella



- Microphthalmia ~20%
- Cataracts ~50%
- Corneal opacity or glaucoma ~5% – 10%
- Retinitis ~5%

Fanaroff, Martin, & Walsh: Ch 36.

Congenital infections

	Rubella	CMV	Toxo
Congenital Heart disease	75	<2	0
LBW	60	60	30
Petechiae	60	60	10
Eye opacities	50	-	-
Retinitis	5	15	85
Cerebral calcification	0	20	40
Bone lesions	30	0	0

Participant Scores

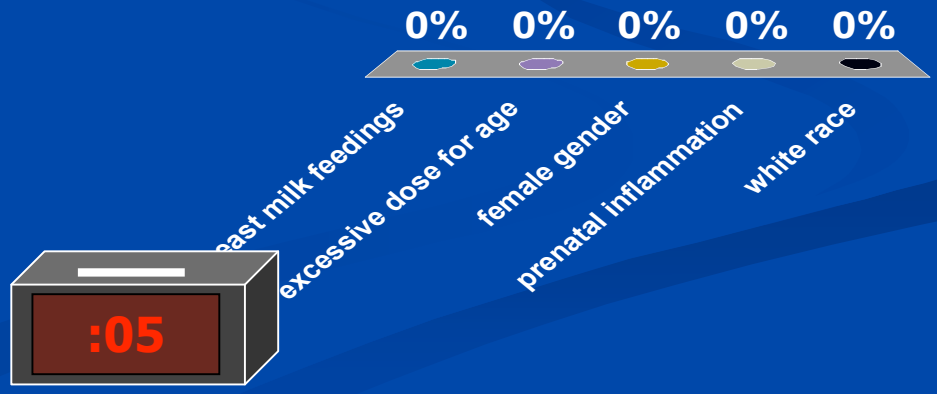
1383.51	Participant 236
1076	Participant 144
1036.41	Participant 148
1033.85	Participant 161
978.94	Participant 164

A 4 week old preterm infant with apnea is receiving caffeine (5 mg/kg per day). The infant is tolerating breast milk feedings and receiving nasal cannula oxygen. During the last week, increasing tachycardia and restlessness is noted. The trough [caffeine] is 34 ug/mL.

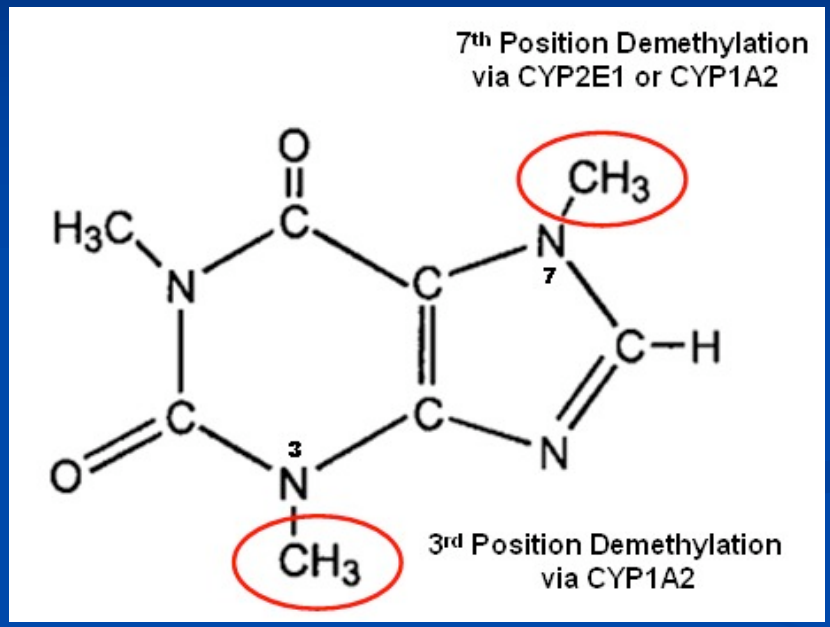
Of the following, the factor MOST likely to predispose this infant to caffeine toxicity is:

- breast milk feedings
- excessive dose for age
- female gender
- prenatal inflammation
- white race

Answer Now



- **Caffeine elimination:**
  - via the urinary tract either unchanged or after conversion to metabolites (CYP1A2 and CYP2E1)



  - premature infant, 85% to 90% is excreted unchanged
  - With maturation, proportion of unchanged caffeine decreases and the proportion of metabolites approaches 100%

Caffeine metabolism interaction

- Infant formulas, but not human milk, induces CYP1A2 expression
  - identity of the molecule(s) unknown
- Breast milk (or those fed breast milk primarily) likely to metabolize and eliminate caffeine more slowly
- Factors not affecting caffeine elimination:
  - sex
  - Races
  - Inflammation

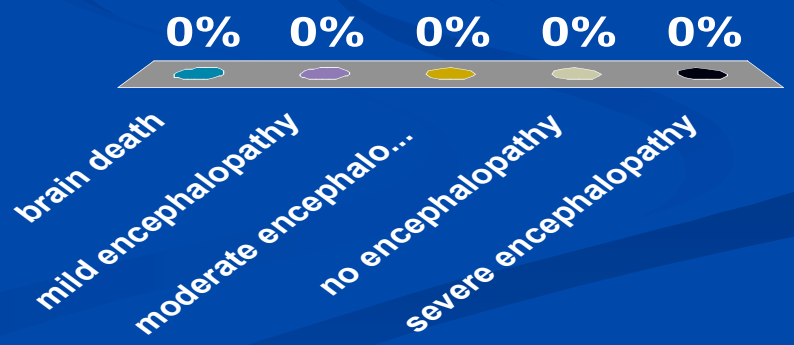
You are called to examine a lethargic 16-hour-old appropriate-for-gestational-age male infant. He had Apgar scores of 1, 4, 6, 6, and 8 at 1, 5, 10, 15, and 20 minutes, respectively. The arterial cord gas revealed a pH of 6.86.

PE:

- **lethargic, but arouses to auditory stimuli**
- **tone decreased**
- **prominent head lag**
- **deep tendon reflexes increased**
- **not interested in feeding**
- **generalized tonic-clonic seizure**

Of the following, the BEST description of neurologic status, based on Sarnat and Sarnat criteria, in this infant, would be:

1. brain death
2. mild encephalopathy
3. moderate encephalopathy
4. no encephalopathy
5. severe encephalopathy



Answer Now

:05

- **Several scales have been developed to assess the severity of HIE. The Sarnat and Sarnat scale divides the stages of HIE into three levels using major clinical features (Table).**

Table. Clinical Staging and Outcome of Hypoxic-Ischemic Encephalopathy*

Severity of Encephalopathy	Mild (Stage I)	Moderate (Stage II)	Severe (Stage III)
Level of consciousness	Alert (hyperalert)	Lethargic	Coma
Muscle tone	Normal	Hypotonic	Flaccid
Tendon reflexes	Increased	Increased	Depressed or absent
Pupils	Mydriasis	Miosis	Variable, often unequal, poor light reflex
Seizures	Absent	Common; focal or multifocal	Uncommon (excluding decerebration)
Electroencephalographic findings	Normal	Low voltage, periodic or paroxysmal	• Early: Periodic pattern with isopotential phases • Later: isopotential
Outcome	Normal	20%-40% abnormal	Death or 100% abnormal

* Adapted from Sarnat and Sarnat (1976) and Roland and Hill (1995).

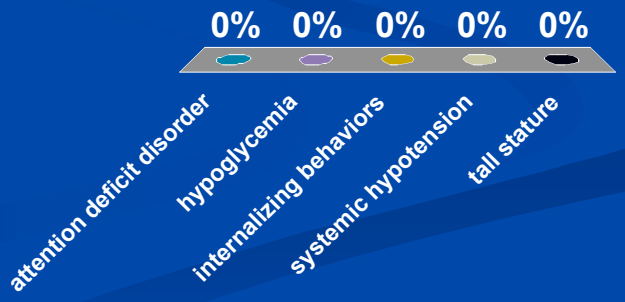
You are meeting with the parents of a low birthweight IUGR infant. They are interested in knowing about the long-term implications of being low birthweight.

Of the following, the problem this infant is MOST likely to have when he reaches adulthood is:

1. attention deficit disorder
2. hypoglycemia
3. internalizing behaviors
4. systemic hypotension
5. tall stature

Answer Now

:05



- **ADHD …**
  - **most frequent abnormal psychiatric outcome … 20%**
  - **inattention problems frequent in preterm infants (eg poor concentration, distractibility, forgetfulness, disorganization, slow mental processing)**
- **Internalizing behaviors (such as anxiety, depression, withdrawal, somatic concerns) and externalizing behaviors (such as delinquency, aggressiveness) … less prevalent**
- **Metabolic syndrome: hyperglycemia (insulin resistance), hypertension, hyperinsulinemia, visceral adiposity, dyslipidemia, ischemic heart disease and type 2 diabetes mellitus**
- **Tall stature … infrequent, tendency for normal to short stature**

ADHD Pathophysiology … Unclear

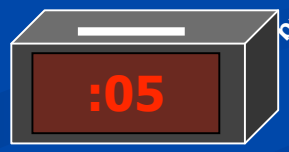
- genetic
- environmental
- fetal
- biochemical
  - dopamine: inhibitory function
  - candidate genes … dopamine D4 receptor gene function important for attention, short-term memory, and executive function … but no clinical correlation with ADHD demonstrated
- medical conditions
- morphologic and functional brain differences:
  - small brain regions or structures important for attention:
    - corpus callosum, basal ganglia (inhibition of automatic
    - responses)
    - frontal lobes (distraction filtering)
    - cerebellar vermis (motivation regulation)

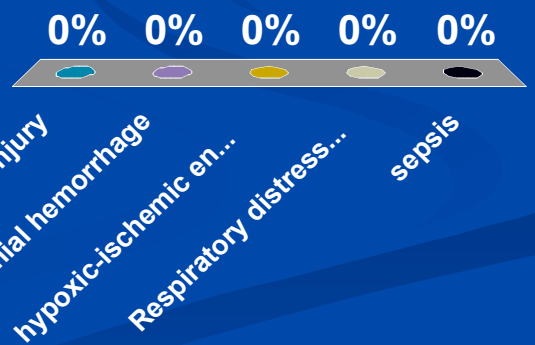
An obstetrician is discussing the risks to the infant of elective cesarean without labor at 37 weeks' gestation.

Of the following, the MOST frequent complication of elective cesarean delivery for this infant is:

- brachial plexus injury
- intracranial hemorrhage
- hypoxic-ischemic encephalopathy
- Respiratory distress syndrome
- sepsis

Answer Now





Cesarean delivery on maternal request (CDMR)

- delivery of a singleton, full-term infant with absence of medical or obstetric indications
- controversial & ~4% to 18% of cesarean births
- moderate levels of evidence:
  - maternal length of stay (increased)
  - maternal hemorrhage (decreased)
  - subsequent placenta accreta or previa (increased)
  - subsequent uterine rupture (increased)
  - neonatal respiratory morbidity (increased)

Respiratory distress syndrome in late preterm and term infants

Gestational Age (Weeks)	Incidence of respiratory distress syndrome (per 1000 infants)	Relative rate compared with following gestation
34	30	2.1
35	14	2.0
36	7.1	3.9
37	1.8	3.0
38	0.6	7.5
39-41	0.08	Reference

Data from Madar J, Richmond S, Hey E. Surfactant-deficient respiratory distress after elective
delivery at 'term.' Acta Paediatr 1999;88:1245

You observe a former 35 weeks' gestation infant taking slow deep breaths while falling asleep after feeding.

Of the following, the respiratory control mechanism MOST likely to contribute to the lung inflation of a neonatal sigh is the sensitivity of the:

1. chemoreceptors of the carotid bodies to hypoxemia
2. chemoreceptors of the ventral medulla to carbon dioxide
3. irritant receptors of the airways to stretch
4. phrenic nerve to distorted intercostal output
5. stretch receptors of the airways to stretch

Answer Now

Pulmonary Reflexes and Control Mechanisms in Neonates	
Head's paradoxical reflex	**Sighs … stimulation of pulmonary irritant receptors**
Carotid body response	**Tachypnea … chemoreceptor stimulation (hypoxemia)**
Ventral medulla response	**Tachypnea … medullary response to [hydrogen ion] or pCO2**
Hering-Breuer reflex	**Apnea … stimulation of pulmonary stretch receptors**
Phrenic nerve stimulation	**Shortened i-time … distortion of intercostal nerves inhibits phrenic nerve**

Head's Paradoxical Reflex

- Rapid lung inflation → deep inspiration, sigh or gasp
- Sometimes followed by apnea
- Mediated by the irritant receptors in mucosa of major airways
- Function: establish and maintain FRC
- Develops later in gestation
- Trigger for neonatal sighs … not known

Participant Scores

1483.51	Participant 236
1161.21	Participant 71
1143.18	Participant 248
1078.61	Participant 170
1076	Participant 144

A term male infant develops temperature instability, hypothermia, and hypoglycemia

Physical examination:

- pudgy cheeks and sagging jowls
- hair and eyebrows are sparse, brittle, and silver-colored
  - microscopic examination of the hair shows pili torti

Family history:

- a brother who had similar hair and eyebrows developed seizures at age 3 months
- He died at age 2 years after progressive neurologic deterioration

Of the following, the trace element whose dysfunctional metabolism is MOST likely to account for the genetic disorder in this family is:

- chromium
- copper
- manganese
- selenium
- zinc

Answer Now

Trace elements= <0.01% of Wt.

- chromium (Cr),
- cobalt, (Co)
- copper (Cu),
- Fluoride (Fl),
- Iodine (I),
- Iron (Fe),
- manganese (Mn),
- Molybdenum (Mo),
- Nickel (Sn),
- selenium (Se),
- Silicon (Si),
- vanadium, and
- zinc (Zn)

- Roles in metabolism:
  - essential components of metalloenzymes
  - cofactors for enzymes

Menkes disease (MD)

- US incidence: 1 in 300,000 live births
- Characteristics:
  - Hair: silvery, sparse, brittle, steel-wool-like
    hair changes may not be present in the newborn
  - Skin: hypopigmented, mottled, doughy, and lax
  - Seizures: begin within first few days or months after birth
  - Developmental: loss of developmental milestones, hypotonia, hypothermia, and lethargy
- Inheritance: X-linked recessive disorder

2005; Nov#10

Menkes disease (MD)

- Derangement of Cu metabolism
  - systemic Cu deficiency due to a defect in intestinal Cu transport
  - Cu essential for brain metabolism
    - cofactor to amyloid precursor protein, dopamine-beta-hydroxylase, superoxide dismutase, and ceruloplasmin
- Treatment:
  - parenteral administration of Cu can modify the course of the disease if started shortly after birth.
- Prognosis: lethal, most die by age 3 yrs

Ambiguous genitalia

An elderly primagravida has amniocentesis showing fetal chromosomes of 46XX.

Fetal ultrasound suggests enlarged adrenal glands.

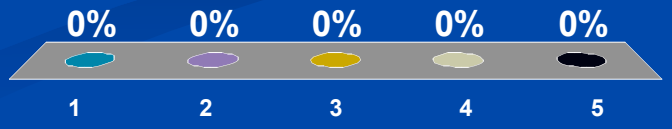
After birth at term, the child has cliteromegaly and posterior labial fusion.

Over the next week, the infant's blood pressure increases, reaching 120 mm Hg systolic by day 10.

A 46, XX, infant with genital virilization & development of hypertension. Of the following, the MOST likely enzymatic deficiency is:

1. 3-beta-hydroxysteroid dehydrogenase deficiency
2. 11-beta-hydroxylase deficiency
3. 17-alpha-hydroxylase deficiency
4. 20,22-desmolase deficiency
5. 21-hydroxylase deficiency

Answer Now



Adrenogenital syndrome:

5 autosomal recessive enzyme deficiencies

Cholesterol

▼ 20,22 Desmolase

Pregnenolone ➔17-hydroxylase ➔ 17-OH Pregnenolone ➔ DHEA

▼ 3-beta-HSD ▼ 3-beta-HSD ▼ 3-beta-HSD

Progesterone ➔17-hydroxylase ➔ 17-OH Progesterone ➔ Androstenedione

▼ 21-hydroxylase ▼ 21-hydroxylase ▼ 21-hydroxylase

Deoxycorticosterone ➔ 11-Deoxycortisol ➔ Androgens & Estrogens

▼ 11-hydroxylase ▼ 11-hydroxylase

SEX

Corticosterone Cortisol

▼

Aldosterone

SUGAR

SALT

(no cortisol…high ACTH → high [precursors])

Adrenogenital syndrome: 11-OH deficiency

Cholesterol

▼ 20,22 Desmolase

Pregnenolone ➔17-hydroxylase ➔ 17-OH Pregnenolone ➔ DHEA

▼ 3-beta-HSD ▼ 3-beta-HSD ▼ 3-beta-HSD

Progesterone ➔17-hydroxylase ➔ 17-OH Progesterone ➔ Androstenedione

▼ 21-hydroxylase ▼ 21-hydroxylase ▼ 21-hydroxylase

Deoxycorticosterone ➔ 11-Deoxycortisol ➔ Androgens & Estrogens

Absent 11-OH

Corticosterone ▼ Aldosterone

Cortisol

SUGAR

SALT

Hypertension

(no cortisol…high ACTH → high [precursors])

SEX

Virilization

Adrenogenital syndrome: 11-OH deficiency overview

- **Deficiency of 11-OH, representing about 5% of cases of congenital adrenal hyperplasia, results in a build up of deoxycorticosterone (DOC), which has a mineralocorticoid effect.**
  - **The enhanced salt retention causes low-renin hypertension.**
  - **An excess of androgens leads to virilization of the female fetus.**

- **Increased concentrations of 11-deoxycortisol (compound S) and DOC suggest the diagnosis.**

- **Treatment with glucocorticoids is monitored using plasma renin activity, blood pressure, and serum concentrations of 11-deoxycortisol and DOC.**

Deoxycorticosterone (DOC) → 11-Deoxycortisol → Androgens & Estrogens

▼ 11-hydroxylase ▼ 11-hydroxylase

Corticosterone Cortisol (no cortisol…high ACTH → high [precursors])

▼

Aldosterone

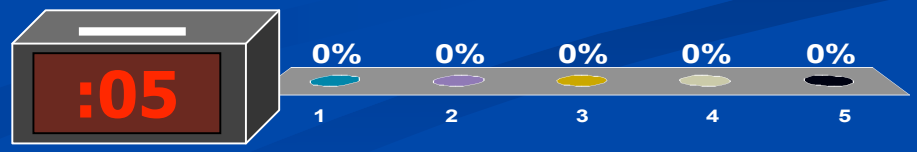
Adrenogenital syndromes: d/d

- 3-beta-Hydroxysteroid dehydrogenase deficiency
  - salt-losing adrenal crises,
  - severe male hypospadius
  - female virilization (via hepatically produced androgens)
- 11-β hydroxylase deficiency –
  - virilization in the female and hypertension
- 17-alpha hydroxylase deficiency –
  - most associated with hypertension and hypogonadism
- 20,22-desmolase (congenital lipoid adrenal hyperplasia),
  - accumulation of cholesterol and lipid in the adrenals that is characteristic,
  - adrenal crises including sodium wasting, hypoglycemia, and hyperpigmentation.
  - Males may have female genitalia, including a blind vaginal pouch, or ambiguous genitalia.
  - Females have normal genitalia.
- 21-hydroxylase deficiency represents > 90% of cases of congenital adrenal hyperplasia
  - Salt loss
  - Female virilization

Of the following, the fetal condition MOST likely to predispose to fetal heart rate (FHR) abnormalities during labor is:

- Down syndrome
- Meningomyelocele
- Potter syndrome
- Prematurity
- trisomy 18

Answer Now



FHR and fetal anomalies

- Down syndrome: no specific predicted effect on FHR
- Meningomyelocele: No specific effect.
- **Potter syndrome: Oligohydramnios, fetal compression make cord patterns more likely, may predispose to compromise.**
- Prematurity: No specific effect
- trisomy 18: No specific effect

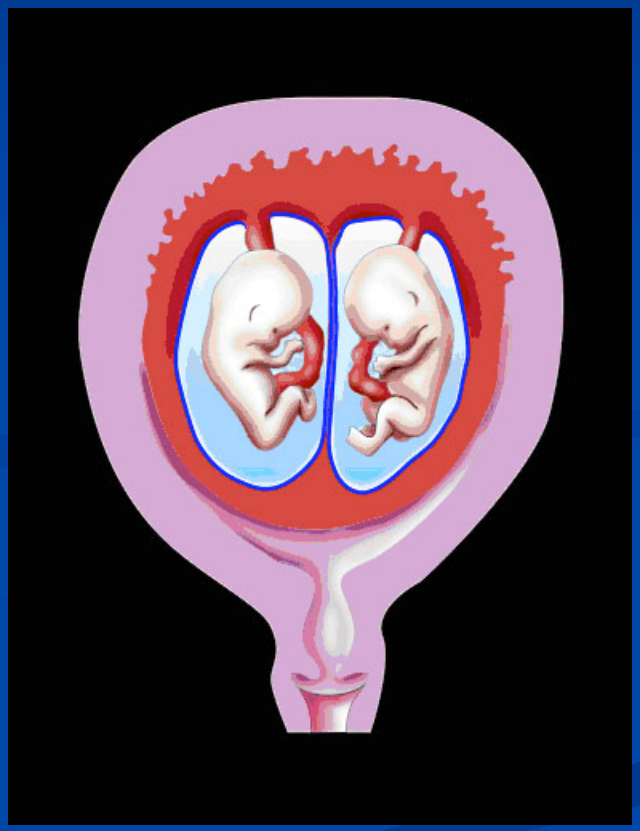
Of the following, the MOST common type of placentation in monozygotic twins is :

- dichorionic/diamniotic with a single placenta
- dichorionic/diamniotic with two fused placentas
- dichorionic/monoamniotic with two separate placentas
- monochorionic/diamniotic with a single placenta
- monochorionic/monoamniotic with a single placenta

Answer Now

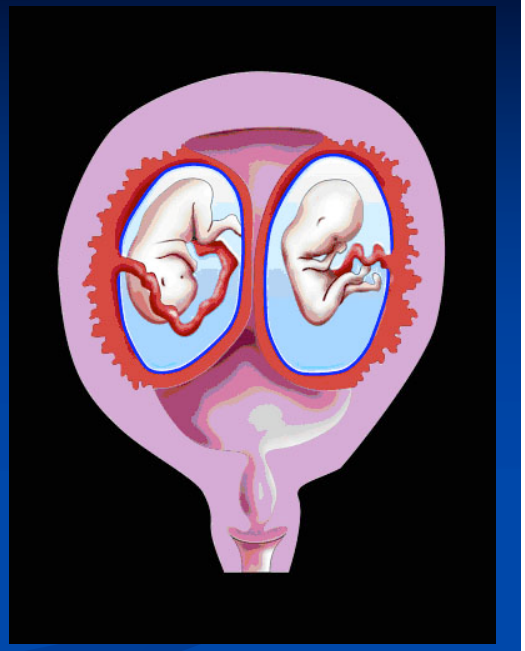
Monozygotic twins: placenta 1

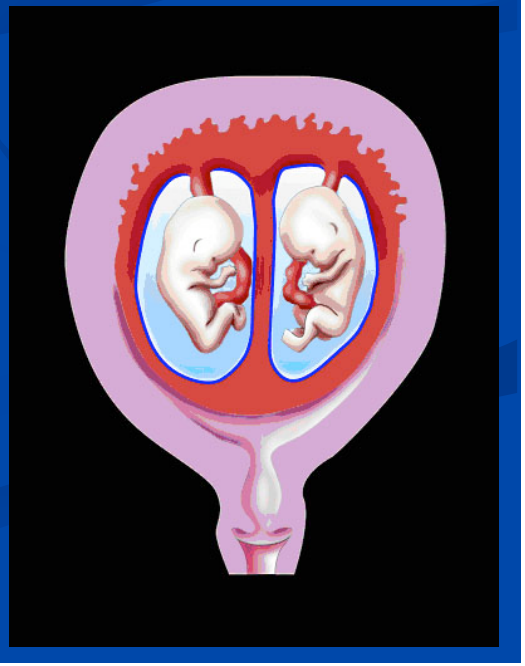
- Monozygotic twins are the result of a single fertilized ovum splitting during the first 2 weeks after conception.
- The timing of the split results in different types of placentation.
  - The most common (70%) form of placentation in monozygotic twins is monochorionic/diamniotic, fertilized ovum splits between 3 and 8 days after fertilization (Fig. 1).
- Monochorionic twin placentas may contain vascular anastomoses that can result in twin-twin transfusion syndrome.



Monozygotic twins: placenta 2

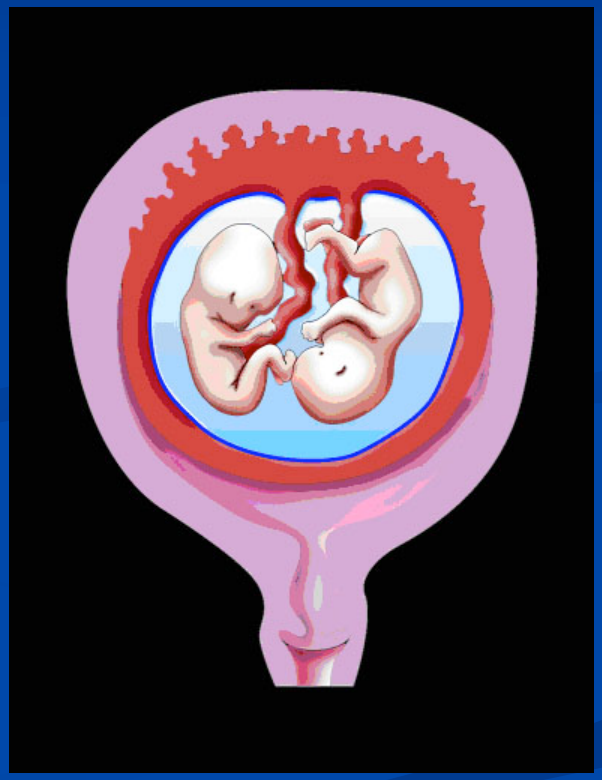
- Dichorionic/diamniotic placentas represent the second most common form of placentation in monozygotic twins, occurring in 30% of monozygotic twins and nearly 100% of dizygotic twins.
- Twins that have dichorionic/diamniotic placentas always have two separate placentas that either can be separate (Fig. 2) or fused (Fig. 3).
- Dichorionic/diamniotic placentas occur in monozygotic twins when the zygote splits between 1 and 3 days after fertilization.
- Because the amniotic cavity develops within the chorion, dichorionic/monoamniotic placentation cannot occur.





Monozygotic twins: placenta 3

- Monochorionic/monoamniotic with a single placenta is a rare form of placentation that occurs in 1% of monozygotic twins (Fig. 4).
  - A monochorionic/monoamniotic placenta develops when the zygote splits between days 9 and 12 after fertilization.
- Twins that have monochorionic/monoamniotic placentation are at the highest risk for fetal demise because umbilical cords can become entangled without a separating membrane.
- If twinning occurs beyond 12 days after fertilization, the monozygotic pair splits only partially, which results in conjoined twins.
  - Conjoined twins always have monochorionic/monoamniotic placentation.



Dizygotic twins: placentation

- When two sperms fertilize two ova, dizygotic twins result.
  - Dizygotic twins nearly always have dichorionic/diamniotic placentation. There is a case report of monochorionic/diamniotic dizygotic twins conceived by in vitro fertilization.
  - Dichorionic/diamniotic placentas may fuse if implantation sites are proximate. Fused placentas can be separated easily after birth.

Seizure & phenobarbital

- A term male infant has repeated seizure activity on the first day after birth.
- Blood glucose, electrolytes, calcium, and magnesium concentrations are within normal limits.
- A pyridoxine infusion does not alter the frequency or severity of the seizures.
- Studies for inborn errors of metabolism are pending.
- Imaging of the brain reveals no cause for the seizures.
- Electroencephalography confirms seizure activity.
- Seizures are stopped with the administration of diazepam.
- Phenobarbital is recommended for long-term maintenance.

Seizure & phenobarbital

- Phenobarbital treatment is started at a dose of 3.5 mg/kg daily.
  - The best estimate of serum half-life for phenobarbital in this infant is 84 hours
  - The therapeutic range is 15 to 40 µg/mL (65-172 µmol/L).

- At what age would you expect >90% steady-state concentration to have been achieved?

Of the following, the EARLIEST time to obtain more than 90% of steady state drug concentration for this dosing of phenobarbital would be around:

1. 3 days of age
2. 7 days of age
3. 10 days of age
4. 14 days of age
5. 28 days of age

Answer Now

Steady state:

- The therapeutic effectiveness of a drug primarily depends on the drug concentration in the body.
- The concentration at any particular time depends on
  - the amount of drug administered,
  - the volume of distribution, and
  - the amount eliminated over time.
- Early on, with the first and subsequent doses, these concentrations vary. There is a tendency for a drug to accumulate over time if the interval between doses is shorter than the time to eliminate the entire dose.
- Eventually, however, with repeated doses the rate of excretion equals the rate of administration. This condition is known as "steady state."

Steady state: expectations

- Rate of excretion equals the rate of accumulation
- Steady state is the condition reached
  - during the continuous administration of a drug in which the plasma concentration of the drug becomes constant,
  - during the periodic administration of a drug in which the plasma concentrations (peak and trough) stay the same with each succeeding dose.

Steady state: time to reach

- The time to achieve steady state depends entirely on the rate of drug elimination (the drug half-life).
- A table modified from Lugo and Ward is presented below that correlates the half-lives of a drug with the steady-state plasma concentrations:.
  - Four to 5 half-lives are needed to reach 94% to 97% of steady state levels.
  - For this case example, this would correspond to approximately 14 days.
  - A loading dose would have helped to achieve therapeutic concentrations faster, but would have complicated the calculation of the time to steady state.

Drug Half-Lives, No.	Steady State Concentration Achieved, %
1	50
2	75
3	88
4	94
5	97

Team Scores

747.66	NPM fellow
738.88	Other nurse
723.19	Advance practice nurse
718.35	Medical student
707.41	Other physician

Participant Scores

1583.51	**Participant 236**
1405.99	**Participant 103**
1278.94	**Participant 164**
1276	**Participant 144**
1264.93	**Participant 125**
1261.21	Participant 71
1243.73	Participant 205
1236.41	Participant 148
1179.3	Participant 26
1178.61	Participant 170

The WINNER IS